OPDIVO is the only PD-1 inhibitor that delivered superior OS vs. chemotherapy in two Phase III studies designed to include PD-L1 expressors and non-expressors with previously treated NSCLC

OPDIVO is indicated for the treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy in adults

OS – overall survival; PD-1 – programmed death-1; PD-L1 – programmed death-ligand 1

Reference: 1. OPDIVO Summary of Product Characteristics.
## IASLC 17th World Conference on Lung Cancer

**December 4–7, 2016**  
**Vienna, Austria**

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*Disclosure Summary*  
*Author Index*
Since Ireland introduced its comprehensive national smoke-free legislation in 2004, many European countries have followed Ireland’s lead, but not all of them. Smoke-free policies are a powerful tool available to governments if they want to prevent cancer and reduce cigarette consumption. Taxation is an effective, highly cost-effective and very powerful tool available to governments if they want to prevent cancer and the many other diseases which are caused by tobacco. Smoke-free policies have other cancer prevention benefits. They discourage young people from starting to smoke, encourage smokers to quit, and help former smokers stay off smoking and promote an attitude of denormalisation of smoking. Smoking has often been regarded as a normal social activity despite the fact that it is addictive, is a cause of great inequality, and contributes significantly to disease, disability, and death. Smoke-free policies can achieve their positive effect by educating about the health benefits, limiting opportunities to smoke, and promoting an attitude of denormalisation of smoking.

**Keywords:** Tobacco Control, Smokefree, Tobacco Taxation, Smoking Cessation

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**SESSION PL03: PRESIDENTIAL SYMPOSIUM**

**TUESDAY, DECEMBER 6, 2016 - 08:35-10:25**

**PL03.02 LUNG CANCER STAGING – CHANGING THE CLINICAL PRACTICE**

Ramón Rami-Porrua
Thoracic Surgery, Hospital Universitari Mutua Terrassa, and Ciberes Lung Cancer Group, Terrassa/Spain

**Introduction:** At the time of the 17th World Conference on Lung Cancer, the 8th edition of the tumor, node and metastasis (TNM) classification of lung cancer will have been published by the Union for International Cancer Control, the American Joint Committee on Cancer and the International Association for the Study of Lung Cancer (IASLC) in their respective staging manuals. The innovations introduced, based on the analyses of the new IASLC database that includes 70,967 evaluable patients with non-small cell lung cancer and 6,189 with small cell lung cancer are described in the table. (1-9) These innovations will lead to some changes in clinical practise that are worth reflecting on. Table. Innovations introduced in the 8th edition of the TNM classification of lung cancer.

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**M component**

- Metastases in thoracic cavity M1a
- Single extrathoracic metastasis M1b
- Multiple extrathoracic metastases M1c
- Other innovations in classification
The T component: Tumor size is a much more relevant prognostic factor than in previous editions and is now a descriptor in all T categories. Therefore, tumor size measurement should be carefully performed because small changes in size mean important changes in prognosis. (2) In part-solid tumors, only the solid/invasive part counts to measure tumor size. (7) The fact that adenocarcinomas—basically invasive adenocarcinomas—

Tm− have their own coding in the TNM classification will increase their awareness. (7) These, together with the smallest coded solid tumors, those of one cm or less in largest dimension—T1a—can become the base from which to study therapeutic options, such as sublobar resections, stereotactic radiotherapy, radiofrequency ablation; tumor biology, including tumorigenesis, growth, tumor density and intensity of the standardized uptake value, as well as molecular profile and genetic signatures. Visceral pleural invasion and its two categories (PL1: invasion beyond its elastic layer; and PL2: invasion of the pleural surface) have been confirmed as important prognostic factors. (2) This means that pathologists should intensively investigate the identification of visceral pleural invasion, and, if it is not evident by the standard hematoxylin and eosine stains, elastic stains should be used, as recommended in the 7th edition of the TNM classification. (10) The N component: Although there will be no changes in the N categories, the analyses for the 8th edition have shown that quantification of nodal disease has prognostic implications. This had already been evident in the 7th edition, when it was found that the number of involved nodal zones was prognostic. For the analyses for the 8th edition have considered the number of involved nodal stations and have found that the more nodal stations involved, the worse the prognosis; and that the tumors of prognosis with involvement of multiple N1 stations was similar to that of tumors with single station N2 without concomitant N1 disease (skip metastases). (3) The findings of the 7th edition already raised the issue of indicating upfront resection in patients with tumors with single N2 zone involvement: their prognosis was shown to be similar to that of tumors with multiple N1 zones. The question will be raised again in the light of the results of the 8th edition. However, in both occasions, the quantification of nodal disease derived from pathological staging of those tumors that had been resected and the resection had been accompanied by a properly performed surgical lymphadenectomy. This is difficult to replicate at clinical staging, the moment at which therapeutic decisions are made, unless a transcervical systematic nodal dissection. This is difficult to replicate at clinical staging, the moment at which therapeutic decisions are made, unless a transcervical systematic nodal dissection. This is difficult to replicate at clinical staging, the moment at which therapeutic decisions are made, unless a transcervical systematic nodal dissection. This is difficult to replicate at clinical staging, the moment at which therapeutic decisions are made, unless a transcervical systematic nodal dissection. This is difficult to replicate at clinical staging, the moment at which therapeutic decisions are made, unless a transcervical systematic nodal dissection.
SESSION PL05: CLOSING PLENARY SESSION: A LIFE IN THORACIC ONCOLOGY - REFLECTIONS FROM GIANTS ON MILESTONES IN THE TREATMENT ADVANCES IN LUNG CANCER
WEDNESDAY, DECEMBER 7, 2016 - 16:00-18:00

PL05.01 PATHOLOGY
Adi Gazdar
Hamon Center for Therapeutic Oncology Research, University of Texas Southwestern Medical Center, Dallas/TX/United States of America

While many regard a pathologist as a physician involved in laboratory diagnosis, by definition Pathology is the science of the study of the origin, nature and course of diseases. This broader definition of pathology, which basically encompasses all of the study of medicine, is what first attracted me to the field. After my residency I joined the NCI as a research pathologist studying viral oncology in rodents. However a few years later John Minna gave me a unique opportunity to return to the study of human cancer when he invited me to appointed the head of the NCI-VA Medical Oncology Branch in Washington, DC, with a focus on lung cancer therapy. Our branch was fortunate to have an outstanding lung pathologist, Mary Matthews who taught me most of what I know about lung pathology. Mary also had a profound effect on the understanding and treatment of lung cancer. In 1973 she established that small cell lung cancer (SCLC) was almost always metastatic at the time of diagnosis, and that surgery was unlikely to be curative. These observations, plus the finding that SCLC showed initial responses to the therapy then currently available, helped establish the fundamental distinction of lung cancers into SCLC and NSCLC categories. The Mary Matthew award for Pathology and Translational Research is one of the distinguished awards of the IASLC and I was fortunate and honored to be the fourth recipient in 2003. John Minna assembled an outstanding group of physicians/scientists many of whom became pioneers in the field of lung cancer. Of interest, all three past and present Chief Executive Officers of the IASLC, Heine Hansen, Paul Bunn and Fred Hirsch, spent time at the NCI-VA Medical Oncology Branch. John preached that new approaches for the therapy of lung cancer were needed, that this would require understanding biology, and to understand biology we needed preclinical models. My job was to establish such models and help "translate" them into clinical care. By the early 1980s we had established and characterized large banks of SCLC cell lines and demonstrated that they expressed the entire neuroendocrine (NE) cell program. The cell lines were widely distributed to the scientific community, and in the absence of reliable transplanted tumors became the major in vivo and in vitro models for the study of lung cancer.

The NCI-VA Medical Oncology Branch later relocated to the Bethesda Naval Hospital in 1988. While at NCI-VA, I had the privilege of working with many wonderful and talented people I have worked with. I am reminded of the quote of Isaac Newton: "If I have seen further than others, it is because I have stood on the shoulders of giants." References 1. Matthews J, Kanhouwa C, Savage TK, et al. Genetically engineered mouse models for neuroendocrine carcinomas of the lung. J Thorac Oncol 2016;11:287-299. 11. Gazdar AF, Savage TK, Johnson JE, et al. The comparative pathology of small cell lung cancer, the SEER database indicates that up to 16% of NSCLC may remain unclassified throughout the USA. For these reasons we developed a molecular classifier for NSCLC that can be applied to formalin fixed paraffin embedded (FFPE) materials and small core biopsies. The assay is highly accurate and quantitative, and also provides information on grading and survival. While SCLC languished for three decades, its recent designation as a reclassifiable cancer by the US Congress has resulted in a dramatic resurrection of interest, funding and achievement. This has highlighted the importance of preclinical models for SCLC. I feel very humbled and privileged to have lived through and contributed to the seminal advances in our understanding of the biology and therapy of lung cancer. This would not have been possible without the many wonderful and talented people I have worked with. I am reminded of the quote of Isaac Newton: "If I have seen further than others, it is because I have stood on the shoulders of giants.”

Keywords: Molecular biology, Translational medicine, Pathology, Lung cancer

PL05.02 SURGERY
Peter Goldstraw
Academic Department of Thoracic Surgery, National Heart and Lung Institute, Imperial College, Dartmouth/United Kingdom

The speaker began his training in Cardiothoracic surgery in 1973 and was appointed as a Consultant in 1979. He will introduce this topic by describing a typical case undergoing surgical treatment for lung cancer in the 1970s, then discuss the patient journey and outcomes at that time. From that basis he will detail the changes in the surgical treatment of lung cancer in the last 40 years. This will include: Changes in the epidemiology of lung cancer. Improvements in pre-operative selection. Improvements in the staging process prior to surgery, during surgery and post-surgery. Differences in surgical approach and the anatomical extent of resection. Changes in the stage classification over that period. The establishment of effective adjuvant therapy. Improved outcomes in morbidity, mortality and survivorship. None of these improvements has been of itself a game changer but collectively they amount to an overall improvement in outcomes and improved quality of life for patients.
Abstracts

PL05. CLOSING PLENARY SESSION: A LIFE IN THORACIC ONCOLOGY - REFLECTIONS FROM GIANTS ON MILESTONES IN THE TREATMENT ADVANCES IN LUNG CANCER

Wednesday, December 7, 2016 - 16:00-18:00


Keywords: lung cancer, radiation oncology, history

PL05.03 RADIO-ONCOLOGY

David Ball
Radiation Oncology, Peter MacCallum Cancer Centre, East Melbourne/Australia

When I commenced training in radiation oncology in 1973, there were no CT scanners, calculations were done with slide rules, and chemotherapy, let alone combined modality therapy, had no established role in the treatment of non-small cell lung cancer. An influential trial published in the Lancet in 1971 had shown no difference in survival whether patients were randomized to radiotherapy, chemotherapy, a combination of the two or a policy of wait-and-see. Yet within 30 years, the standard of care for patients with inoperable non-small cell lung cancer has changed dramatically. Improved understanding of the natural history and biology documented above will shamefully be restricted to only a fraction of our patients and the detected fusions were confirmed by FISH. From March 2015, patients and the detected fusions were confirmed by FISH. From March 2015, EGFR-RTKs were analyzed for ALK/ROS1/RET fusions using RT-PCR in EGFR –Mt negative patients and the detected fusions were confirmed by FISH. From March 2015, EGFR-RTKs were analyzed for ALK/ROS1/RET fusions using RT-PCR in EGFR –Mt negative patients. From March 2015, we have shown no difference in survival whether patients were randomized to radiotherapy, chemotherapy, or a combination of the two. The techniques to demonstrate this process are mandatory for successful patient selection in the treatment with anti-PD-1 antibody. The most important thing will be the function of killer T lymphocytes which can respond to target antigens and to kill tumor cells. The best method may be quantitative measurements of cytotoxicity in killer T cell on tumor cells. The techniques to demonstrate this process are mandatory for successful patient selection in the treatment with anti-PD-1 antibody.

PL05.04 TRANSLATIONAL LUNG CANCER RESEARCH

Nagahiro Saijo
Japanese Society of Medical Oncology, Tokyo/Japan

Lung cancer is a leading cause of cancer death in the world. The survival benefit of chemotherapy was rarely observed in NSCLC until the development of Cisplatin. Platinum doublets including 2nd/3rd generation cytotoxic drugs showed minor prolongation of survival but the effect reached a plateau. JCOG conducted key RCTs to develop new standards against SCLC but a breakthrough has not been observed yet. Two recent major therapeutic advancements in NSCLC are immunotherapies to inhibit immune checkpoints and development of targeted drugs for driver mutations.

Translational Research in immune Checkpoint inhibitors: Immunotherapy of cancer has a long history without success because of wrong strategy of immune stimulation with non-specific immunostimulators, biological response modifiers and recently by peptide antigens. After introduction of idea on immune checkpoint inhibition by Dr. James Allison, the studies of this fields were dramatically activated. Currently two anti-PD-1 antibodies such as Nivolumab and Pembrolizumab have been approved for the treatment of NSCLC based on reproducible effects of tumor shrinkage and survival benefit. In second line treatment, both murine and humanized antibodies significantly improved survival compared with standard care of cytotoxic chemotherapy irrespective of patient selection. Recent press release announced that Nivolumab failed to demonstrate benefit for PFS compared to cytotoxic chemotherapy (CheckMate-026), on the other hand Pembrolizumab demonstrated superior PFS compared to platinum doublet therapy. Both of the trials patient selection was done based on PD-L1 expression in lung cancer cells. In spite of positive data on survival, RR in various trials against advanced NSCLC with or without prior chemotherapy ranges from 15-25% for both drugs and median survival is almost same in anti-PD1 Ab and cytotoxic drugs. The most important issue will be to concentrate on radiation therapy to eradicate the responsive patient population or how to eliminate in effective patients. Although there is a tendency of correlation between PD-L1 expression and objective response/survival, responders to Ab are experienced even in PD-L1 negative patients. There are many problems in PD-L1 screening. There is no comparative data of various PD-L1 tests used in various clinical trials. Each PD-L1 test uses different antibody. Each test uses a different definition and cut off point that defines PD-1 positivity. There is no data on best sample, paraffin-fixed vs fresh tissue, primary tumour vs metastatic tissue. PD-L1 expression is not stable and influenced by many factors. There is no standard method for validation and standardization. In tumor cells, mutation burden may influence on antigenicity. In colorectal cancer, microsatellite instability has related with response to anti-PD-1 antibody, but it is not yet clear whether mutation burden really increases antigenicity. CD8 lymphocytes infiltration is also considered to be one of the paclitaxel, but it is not yet clear whether mutation burden really increases antigenicity. CD8 lymphocytes infiltration is also considered a good biomarker for anti-PD-1/2 antibody. It is too objective and seems to be quite difficult to quantify CD8 lymphocytes infiltration. The most important thing will be the function of killer T lymphocytes which can respond to target antigens and to kill tumor cells. The best method may be quantitative measurements of cytotoxicity in killer T cell on tumor cells. The techniques to demonstrate this process are mandatory for successful patient selection in the treatment with anti-PD-1 antibody.

Translational Drug Development for Precision Medicine

Recent development of molecular target drugs in lung cancer really reflects progress of translational science. EGFR-RTKs are one of the most important drugs and changed concept of treatment of lung cancer. Finding on many rare driver mutations forced to reclassify lung cancer to various genomic subtypes. Innovative technologies for genomic medicine changes one size fit medicine to precision medicine. For discovery of drugs to each genomic subtype of lung cancer, nation-wide and wide-screening network should be established. In Japan LC-SCRUM Japan led by Dr. Koichi Goto, National Cancer Center Hospital East, started in February 2013 to find out new seeds against lung cancer by the support of government. At the beginning, tumor tissues were analyzed for ALK/ROS1/RET fusions using RT-PCR in EGFR –Mt negative patients and the detected fusions were confirmed by FISH. From March 2015, multiplex diagnostic kit using NGS was introduced and this project expanded as SCRUM-Japan including other histological types of lung cancer such as SQ and 5M as well as GI malignancies.

14 pharmaceutical companies started to support this project. No. of institutions joined in the network increased to 200 in Non-SQ NSCLC, 159 and 96 for SQ and SM, respectively on March, 2016. More than 2,500 samples were analyzed. Rare mutations including ROSD(91), RET(S4) and ALK(40) fusions, ERBB2 mutation/amplification(48), BRAF mutation(16), MET amplification/
and histology. In parallel, the adjuvant UFT meta-analysis also confirmed a significant advantage of the drug compared to control in 2003 (Japanese patients \(p<0.001\)). The individual-data-based meta-analysis was updated in 2007. It confirmed the significant effect of postoperative chemotherapy, with or without postoperative radiotherapy. 

Adjuvant chemotherapy: Several phase II trials have been carried out in the 80’s to evaluate the benefit of preoperative chemotherapy in operable NSCLC with encouraging results. In the mid 90’s, 2 randomized phase III trials had a significant impact on the medical community due to the results. Both studies included 60 stage IIIB patients and were interrupted after positive interim results were observed. Only two published randomized phase III studies comparing front-line surgery to pre-operative chemotherapy followed by surgery accrued the number of patients that were initially planned: a French study that included 373 patients and the Medical Research Council LU22 trial that included 519 patients. None of the large randomized studies could demonstrate a significant advantage in favor of pre-operative chemotherapy. A recent individual patient-data meta-analysis of pre-operative chemotherapy trials has included 2385 patients from 13 trials. A HR of 0.87 (CI 95%, 0.7–0.96, \(p=0.007\)) was observed, equivalent to an absolute improvement in survival of 5% at 5 years, similar to the benefit observed with postoperative chemotherapy. Preoperative or postoperative chemotherapy? A comparison of preoperative versus postoperative chemotherapy has been did not show any difference. In fact, the key issue may be to determine which patients should be treated with adjuvant and/or neo-adjuvant therapy. The neo-adjuvant approach offers a unique opportunity to test new drugs and to compare the tumor characteristics prior to and following induction therapy. Developing molecular based therapeutic strategies will certainly be one of the major challenges in the next few years. Several randomized adjuvant studies have recently been initiated in Europe and in America, based on the molecular characteristics of patients tumor. In conclusion, chemotherapy remains the main systemic treatment for most patients with lung cancer and the only one able to increase the cure rate. Unfortunately, very few drugs have been developed in the last decade in spite of a clear unmet need. A better individual selection of drugs/drug combinations according to pharmacogenomic data might encourage the community to optimize the use of cytotoxic agents.

Keywords: Chemotherapy NSCLC

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**PL05.05 CHEMOTHERAPY**

**Thierry Le Chevallier**

Medicine, Gustave Roussy Hospital, Villejuif/France

Chemotherapy has long been the only available systemic treatment for Non-Small Cell lung Cancer. In the late 70’s, there were a multitude of triplets and quadruplets with response rates ranging from 20-35% in patients with stage IV disease. For instance, cisplatin, a cytotoxic agent initially developed for germ-cell tumors, showed some activity, mostly when combined with a vinca-alkaloid or with etoposide. At the time Vinorelbine was registered by the FDA in 1994, alone or in combination with cisplatin, only 3 drugs were approved for NSCLC, nitrogen mustard, methotrexate and doxorubicin! Most systematic and individual-data based meta-analysis of chemotherapy in NSCLC in 1995 established the superiority of chemotherapy over supportive care in patients with advanced NSCLC. These results have been recently updated and confirmed in 2714 patients from 16 trials with an overall survival benefit of 9% at 1 year. Chemotherapy also improves quality of life and symptom control in patients with good performance status. It is classically recommended to use platin compounds (mostly cisplatin and carboplatin) in combination with third generation agents including vinorelbine, gemcitabine, taxanes (paclitaxel, docetaxel, nab-paclitaxel) or pemetrexed (in non-squamous NSCLC). Integrating palliative care at an early stage of the treatment also prolongs survival and improves quality of life. Second line chemotherapy with docetaxel or pemetrexed has also been demonstrated active even if the benefit on overall survival remains modest. The use of biological markers such as ERCC1, RRMI, beta-tubulin or thymidylate synthase has not yet proven efficacy in NSCLC. It is not clear if the association of a cytotoxic agent and a molecular agent (targeted) could overcome the resistance of NSCLC. In parallel, the adjuvant UFT meta-analysis also confirmed a significant advantage of the drug compared to control in 2003 (Japanese patients \(p<0.001\)). The individual-data-based meta-analysis was updated in 2007. It confirmed the significant effect of postoperative chemotherapy, with or without postoperative radiotherapy. 

**Keywords:** Chemotherapy NSCLC

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**PL05.07 A WISE MAN’S CONCLUSION**

**Lawrence Einhorn**

Medicine, Indiana University, Indianapolis/IN/United States of America

The past decade has seen more advances in diagnosis and management of lung cancer than were available in the previous 30 years. Fifty years ago, the association of cigarette smoking with lung cancer was firmly established by the Surgeon General’s report in the United States. During the past decade, major efforts by IASLC and other organizations have greatly decreased the use of tobacco and, thus, we will see a decrease in morbidity and mortality from lung cancer. However, in the United States last year, there were still 228,000 new diagnoses and 159,000 deaths from lung cancer. It remains the number one cause of cancer death in both American men and women, and the same is true in most developed and developing countries. Over 28% of all cases of cancer death in the United States are due to lung cancer. IASLC has been a leader in updating the TNM classification for non-small cell lung cancer. This allows for uniformity of data results in surgical and adjuvant studies. Cisplatin-based adjuvant chemotherapy has been demonstrated to improve the surgical cure rate by 5-10%. In the future, we hope to be able to identify by molecular, rather than just clinical characteristics, those patients with resected lung cancer who are cured with surgery and do not need to be subjected to adjuvant chemotherapy, as has been similarly accomplished in breast cancer. Also, we hope to have better definition of tumors that are inherently platinum resistant and, therefore, would need alternative strategies to try to improve the surgical cure rate. For the last two decades of the 20th century, chemotherapy has been the backbone for treatment of stage IVB lung cancer. Most studies have been built around platinum combination chemotherapy. Earlier studies pre-platinum utilized inactiv drugs such as cyclophosphamide and doxorubicin. In the 1980s, cisplatin and etoposide was a common platinum doublet, and in the 1990’s, carboplatin + paclitaxel. A review of phase III trials in North America from 1973-1994 demonstrated very sobering results. Thirty-three trials in 6,434 patients were performed and 23 of these 33 included a platinum compound. Only 5 of the 33 trials demonstrated a statistically significant difference in survival with a median increase of 2 months (range 0.7 to 2.7 months). It thus became clear that adjuvant chemotherapy had no advantage in survival for all patients the same chemotherapy. Mostest success was seen by adding Bevacizumab to carboplatin + paclitaxel. Major advances have been made during the past decade with the identification of specific mutations that can be therapeutically exploited. EGFR and ALK were the first to be
identified and subsequently ROS-1. Molecular targeted agents demonstrated spectacular responses in the great majority of patients, compared to the usual 25% brief responses that were achieved previously with platinum-based combination chemotherapy. These driver mutations were predominantly in adenocarcinomas and non-smokers or never smokers. More recent mutations have included smokers and non-smokers such as BRAF V600E and MET Exon-14 skipping mutation which can be seen in smokers as well as non-smokers. During the past five years, immunotherapy has been an exciting new addition to the armamentarium for treatment of patients with metastatic lung cancer. Immune checkpoint inhibitors are still in the nascent phase and the optimal duration of therapy for stage IVB disease, combination with other immunotherapeutic agents, chemotherapy, or radiotherapy, as well as use of adjuvant therapy, will be awaited with eager anticipation. Exciting new technology such as CRISPR-cas9 to gene edit PD-1 holds great potential future promise to make these immune checkpoint inhibitors more effective in a larger percentage of patients with lung cancer, as well as those responses being more durable.

**Keywords:** lung cancer, chemotherapy, immunotherapy, new agents
Abstracts
EDUCATION SESSIONS
SESSION ED01: BIOLOGY OF LUNG CANCER
MONDAY, DECEMBER 5, 2016 - 11:00-12:30
ED01.02 TOBACCO CARCINOGENS AND LUNG CANCER
SUSCEPTIBILITY
Stephen Hecht 1, S. Lani Park2, Steven Carmella1, Daniel Stram2, Christopher
Haiman2, Loic Le Marchand3, Sharon Murphy1, Jian-Min Yuan4
1
Masonic Cancer Center, University of Minnesota, Minneapolis/MN/United States of
America, 2University of Southern California Keck School of Medicine, Los Angeles/
CA/United States of America, 3Cancer Research Center of Hawai’I, University of
Hawai’I, Honolulu/AL/United States of America, 4University of Pittsburgh Cancer
Institute, University of Pittsburgh, Pittsburgh/PA/United States of America

While cigarette smoking is clearly the major cause of lung cancer, only 11% of
female and 24% of male lifetime smokers will get lung cancer by age 85 or
greater, and this relatively small percentage is not due to competing causes of
death from smoking (1) The major goal of the research approach discussed in
this presentation is to identify individuals who are highly susceptible to the
carcinogenic effects of cigarette smoke. These individuals would be
candidates for intensive lung cancer surveillance and screening, increasing the
probability of detection of a tumor at an early stage. We are not proposing
methods for early detection of tumors such as the identification of
metabolites or proteins characteristic of lung tumors, but rather early
identification of susceptible individuals. While there are already algorithms
relating various parameters to lung cancer susceptibility, they are mostly
retrospective in nature, with pack-years of cigarette smoking being a major
prognostic factor (2,3). Thus, these algorithms are typically applied to
subjects who are older, when the process may be more advanced. Our ultimate
goal is to develop a risk model that is prospective in nature. Overall, there
would be a greater probability of success if one could identify high risk
individuals early in the carcinogenic process. Even if this were effective in only
10% of tobacco users, the outcome could be prevention of more than 15,000
lung cancer deaths per year in the U.S. alone and massive financial savings.
Among the more than 7,000 identified chemical compounds in cigarette
smoke, there are 72 fully characterized carcinogens among which at least 20
are known to cause lung tumors in laboratory animals (4,5). Important among
the lung carcinogens are polycyclic aromatic hydrocarbons (PAH) such as
benzo[a]pyrene, tobacco-specific nitrosamines such as
4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), and volatiles such as
1,3-butadiene. Other related volatile compounds that may contribute to the
carcinogenic process include acrolein, crotonaldehyde, and benzene. Perhaps
the most important compound in tobacco smoke is nicotine – while not a
carcinogen, it is the addictive constituent of smoke that causes people to
continue to inhale this incredibly unhealthy mixture. In pursuit of our goal of
identifying smokers susceptible to lung cancer, we have focused on several
tobacco smoke toxicant and carcinogen parent substances and metabolites in
urine (6). Thus, we and others have developed and applied analytically
validated mass spectrometric methods for total nicotine equivalents (the sum
of nicotine and six metabolites: nicotine glucuronide, cotinine, cotinine
glucuronide, 3’-hydroxycotinine and its glucuronide, and nicotine-N -oxide);
total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL), a metabolite of
NNK; phenanthrene tetraol (PheT) and 3-hydroxyphenanthrene (3-PheOH),
metabolites of a representative PAH; S -phenylmercapturic acid (SPMA), a
metabolite of the carcinogen benzene; 3-hydroxypropylmercapturic acid
(HPMA), a metabolite of acrolein; and 3-hydroxy-1-methylpropylmercapturic
acid (HMPMA), a metabolite of crotonaldehyde. We have collaborated with
epidemiologists to evaluate the relationship of these urinary metabolites to
cancer, as determined in prospective cohort studies. These studies collect and
store bio-samples from large numbers of healthy subjects, then follow the
subjects until sufficient numbers of cancer cases occur for statistical analysis.
Samples from the cases and matched controls without cancer are retrieved
from biorepositories and analyzed for specific biomarkers. The results of
these studies have been reviewed (7,8). In summary, statistically significant
relationships of urinary total cotinine (cotinine plus its glucuronide, the major
metabolite of nicotine), total NNAL, and PheT with lung cancer risk were
observed among male smokers in Shanghai. Urinary total cotinine and total
NNAL were related to lung cancer risk in a study of male and female smokers in
Singapore, and total NNAL in serum was related to lung cancer risk in a study
of male and female smokers in the U.S. (7,8). Levels of urinary SPMA , HPMA,
and HMPMA were not independently related to lung cancer in the Shanghai
study. These results indicate that total cotinine, total NNAL, and PheT are
possible biomarkers of lung cancer risk. We are also collaborating with
scientists from the Multiethnic Cohort study, a prospective cohort study
investigating the association of genetic and lifestyle factors with chronic
diseases in a population with diverse ethnic backgrounds. They have reported
that, for the same number of cigarettes smoked, and particularly at lower
levels of smoking, African Americans and Native Hawaiians have a higher risk
for lung cancer than Whites while Latinos and Japanese Americans have a
lower risk (9). We are investigating the mechanistic basis for these remarkable

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differences. We analyzed urine samples from 300-700 subjects per group for
total nicotine equivalents, total NNAL, PheT, 3-PheOH, SPMA, HPMA, and
HMPMA. The results demonstrated that African Americans, although smoking
fewer cigarettes per day than any of the other groups except Latinos, had
significantly higher levels of total nicotine equivalents, total NNAL, PheT,
3-PheOH, and SPMA compared to Whites while Japanese Americans had
significantly lower levels of most of these biomarkers than Whites. The
relatively low level of urinary total nicotine equivalents in the Japanese
American smokers was related to a high prevalence of CYP2A6 polymorphisms
in this group (10). CYP2A6 is the primary catalyst of nicotine metabolism and
the CYP2A6 alleles common in Japanese Americans code for low activity and
non-functional enzyme. Therefore, Japanese Americans on the average have
more unchanged nicotine circulating and will not need to obtain as much
nicotine per cigarette. The biomarker profiles of Native Hawaiians and Latinos
did not clearly relate to their relative lung cancer risks, but Native Hawaiians
had high levels of the acrolein biomarker HPMA compared to other groups
while those of Latinos were low. These results provide important new data
pertinent to the relatively high risk of African Americans and the lower risk of
Japanese Americans for lung cancer. Collectively, our results support the use
of urinary nicotine metabolites, total NNAL, and PheT as biomarkers of lung
cancer risk in cigarette smokers. Further studies are required to produce a
reliably predictive algorithm for lung cancer susceptibility in cigarette
smokers. These studies are likely to require the analysis of DNA adduct levels
and to incorporate genetic and epigenetic information. Reference List 1.
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determinants of CYP2A6 activity across racial/ethnic groups with different
risk of lung cancer and effect on their smoking behavior. Carcinogenesis in
press.
Keywords: tobacco carcinogens, polycyclic aromatic hydrocarbons,
4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)

ED01: BIOLOGY OF LUNG CANCER
MONDAY, DECEMBER 5, 2016 - 11:00-12:30

ED01.03 INSIGHTS FROM TCGA
Bharath Ganesh1, Siddhartha Devarakonda2, Ramaswamy Govindan3
1

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2

Advances in sequencing technologies have made it possible to characterize
and catalogue genomic alterations in several cancers in an unbiased manner.
Multiple individual groups and large-scale consortia such as The Cancer
Genomic Atlas (TCGA), have sequenced close to a thousand lung cancer
samples to date. 1-8 Apart from furthering our understanding of the frequently
altered pathways in common histological subtypes of lung cancer, data from
these studies have also highlighted the molecular heterogeneity underlying
this disease. Investigators from TCGA initially reported genomic,
transcriptomic, methylation and copy-number alterations in 230
adenocarcinoma (LUAD) and 178 squamous cell carcinoma (SQCC)
samples.1,2 An updated analysis, that included a total of 660 LUAD and 484
SQCC samples, was subsequently published in early 2016.9 While the majority
of lung cancer patients have a history of cigarette smoking, nearly 10% of
patients are lifelong never-smokers.3Lung cancers that arise in smokers
exhibit some of the highest mutational burdens across all human cancers (8-10
mutations/Mb). The vast majority of these mutations are C>A transversions.

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On the contrary, tumors from never smokers demonstrate a much lower mutational burden (0.8-1 mutations/Mb) and are enriched for C-to-T transitions. 1,2 Single nucleotide variations (SNVs) and copy number alterations (CNAs) While both LUAD and SQCC show frequent inactivation of the tumor suppressors TP53 and CDKN2A, these alterations are considerably more common in SQCC. CDKN2A harbors the loci for two isoforms, p14ARF and p16INK4A, and is inactivated in SQCC through homozygous deletion (29%), methylation (21%), inactivating mutations (18%), or exon 1b skipping (4%). 3,4 These findings demonstrate the importance of multiple pathways (SOX2, TP53, NOTCH1, etc.) in 44% of samples. 1,2 Kras is the most commonly mutated oncogene in LUAD, followed by EGRF, BRAF, PIK3CA, and MET. The majority of EGFR mutations in LUAD are targetable (L858R or exon 19 deletion) with tyrosine kinase inhibitors (TKIs). In contrast, such alterations are absent in SQCC. Two SQCC samples however demonstrated L858R mutations in EGFR, which are potentially targetable with TKIs. 1,2 Although SQCC and LUAD shared several CNAs at the chromosomal arm level, amplification of 3q was frequent in SQCC. This region harbors important oncogenes such as SOX2, PIK3CA, and TP53. LUADs frequently showed mutations that were classified as oncogene positive, including RAS, EGFR. 1,2 Oncogenic activation of kinases such as ALK, ROS1, and RET through rearrangement has been well described in LUAD, and these fusions are targetable with TKIs. These fusions were seen in 1-2% (ALK: 3/230, ROS1: 4/230, and RET: 2/230) of LUAD samples. 1,2,3,4 Transcriptome analyses have also enabled a reclassification of LUAD and SQCC into three and four distinct subtypes, respectively. LUAD samples can be categorized as terminal respiratory unit (enriched for SQCCs into three and four distinct subtypes, respectively. LUAD samples can be categorized as terminal respiratory unit (enriched for oncogene positive) negative sample cohort showed enrichment for RIT1 and NFI mutations. Given the role of RIT1 and NFI in RTK/RAS/RAF signaling, samples with these mutations were reclassified as oncogene positive, increasing the overall percentage of oncogene positive samples in LUAD to 76%. Nearly 69% of SQCC samples showed alterations in genes regulating PIK3/AKT, or RTK/RAS signaling. 1,2 The inability to readily identify an oncogenic driver in nearly a third of sequenced samples highlights the need for greater powering of subsequent studies to identify novel low frequency genomic alterations. For instance, previously uncharacterized alterations in the RTK/RAS/RAF pathway were observed in RASAI, SDS in the updated TCGA analysis which analyzed a much larger cohort of samples. 1,2 Overall, despite showing a few similarities, the patterns of LUAD and SQCC revealed prominent differences between the genomic landscapes of these subtypes. These subtypes have more of their alterations in common with other cancers than with one another. SQCCs more closely resembled head and neck squamous cell and bladder cancer, while LUAD resembled glioblastoma multiforme and colorectal cancer in this regard. 1 Immunotherapies The vast majority of lung cancers do not harbor alterations that are targetable by TKIs. 1,2 Immune checkpoint inhibitors are approved for use in patients with metastatic NSCLC. There is a need to develop novel predictive biomarkers to identify those who are likely to respond to immune checkpoint inhibitors. While the majority of randomised trials have been correlated with better response to checkpoint inhibitors. Furthermore, using exome and transcriptome sequencing and sophisticated bioinformatics, it is now possible to identify mutated and expressed genes that could potentially serve as a trigger for immune response (so called neoantigens) once immune checkpoints like programed death 1 (PD1) are inhibited. Vasen and colleagues performed a neoantigen and clonality analysis on TCGA samples to examine characteristics such as neoantigen burden and intratumor heterogeneity (ITH), and their impact on survival. In LUAD, a higher neoantigen burden was significantly associated with longer survival. Although not statistically significant, there was a trend towards longer survival in molecularly homogeneous tumors (<1% ITH) as opposed to heterogeneous tumors. The updated TCGA analysis showed that 47% of LUAD and 53% of SQCC samples exhibited at least five predicted neoantigens. Efforts are underway to validate vaccine therapy using personalized recognized neoantigens in lung cancer and other malignancies. Outcomes for patients with advanced lung cancer are likely to improve in the near future with further advances in genome sequencing, molecularly targeted therapies and immunotherapies. 1 References: 1. Network CGAR. Comprehensive molecular profiling of lung adenocarcinoma. Nature 2014;513:543-50. 2. Network CGAR. Comprehensive genomic characterization of lung adenocarcinoma. Nature 2012;489:519-25. 3. Govindan R, Ding L, Griffin T, et al. Genomic landscape of non-small cell lung cancer in smokers and never-smokers. Cell 2012;150:1121-34. 4. Imielinski M, Berger AH, Hammerness P, et al. Mapping the hallmarks of lung adenocarcinoma with massively parallel sequencing. Cell 2012;150:1107-20. 5. George A, et al. Comprehensive genomic profiles of small cell lung cancer. Nature 2015;526;47-53. 6. Rudin CM, Durinck S, Stawski EW, et al. 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Clonal neoantigens elicit T cell immunoreactivity and sensitivity to immune checkpoint blockade. Science 2016;351:1463-9. Keywords: TCGA, Genomics, sequencing.
care with serious illness and the focus of Palliative Care is on providing relief from symptom and improving the quality of life of patients. Palliative Care is not End-of-Life or hospice but encompasses both. There is a dichotomy in the principle of medical care in cancer which single mindedly focuses on attempts to cure every patient at every stage. Recognition of the importance of symptom control and other aspects of Palliative care from diagnosis through dying process has been growing. Patients should not have to choose between treatment with curative intent or comfort care. There is need for both in varying degrees throughout the course of a patient whose eventful outcome is survival or death. The goal is to maintain the best possible quality of life allowing the patients to choose whatever treatment they so wish while also meeting the needs of advanced disease through adequate symptom control. This goal is most often not met. For at least half of those patients doing from curative care whom are elderly and many vulnerable deaths entail a spectrum of symptoms including pain, labored breathing, distress, nausea, confusion, and other physical and psychological conditions that go untreated and vastly diminishes the quality of remaining days. The patient is not the only one who suffers; family, care givers undergo unrelieved emotion and financial burden. This should be integrated with the concept of the patients’ who are terminally ill. A major problem in Palliative care is the under recognition, under diagnosis and thus undertreatment of the patients with significant stress ranging from existential anguish, anxiety and depression. Living with and eventually dying from a chronic illness runs substantial cost for patients, family, society and cost of the dying from cancer are 20% higher than average costs. Inadequacy of Palliative and End of Life care springs not from a single cause of a sector of society the separation of palliative and hospice care from potentially life prolonging treatment within the health care system, which is both influenced by and affects reimbursement policy, inadequate training of health care personnel in symptom management and other palliative care skills; inadequate standards of care and lack of accountability in caring for dying patients; disparities in care, even when available, for ethnic and socioeconomic segments of the population; lack of public dealing with the public about end of life care; lack of reliable data on the quality of life and the quality of care of patients dying from cancer (as well as other chronic diseases); and low level of public sector investment in palliative and end of life care research and training. This is not to suggest that there is no relevant ongoing research of the relevant education and training program there are - but the efforts are not coordinated and there is no focus for these activities in the Government agencies. What has resulted is under funding, lack of training and lack of research, leadership, with no sustained program for developing and disseminating Palliative treatment. Care for those approaching death is an integral and important part of patient care which means that correcting problems will require change at the system level. The health care community has special responsibility for educating itself and others about the identification, management, and discussion of the last stage of fatal medical problems. Although health care professionals may not have a central presence in the lives of some people who are dying, many others draw heavily on physicians, nurses, social workers, and others for care — and caring. Thus, health care professionals are inescapably responsible for educating themselves and helping to educate the broader community about good care for dying patients and their families. More and better research is needed to increase our understanding of the clinical, cultural, organizational, and other practices or perspectives that can improve care for those approaching death. The knowledge base for good end of life care has enormous gaps and is neglected in the design and funding of biomedical, clinical, psychosocial, and health services research. Time is now to integrate Palliative care with mainstream care in cancer.

Keywords: Palliative-care, Cancer-care, Improving Cancer-care, End-of-Life-care

ED02.04 PALLIATIVE CARE IN SOUTH-EAST ASIA

Richard Lim

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Southeast Asia comprises of 10 main countries including Malaysia, Indonesia, Thailand, Philippines, Singapore, Brunei, Cambodia, Laos, Myanmar and Vietnam. The concept of palliative care first developed around the mid-1980s in Singapore and the Philippines and later in the 1990s in Malaysia, Thailand and Indonesia. In other countries such as Brunei, Cambodia, Myanmar, Vietnam and Laos, this concept has been developing more rapidly over the past 10 years. Levels of development of palliative care in Southeast Asia are highly variable depending very much upon factors such as availability of medical resources, funding, geography, demographics and the priorities of the country’s leadership. In 2011, the Worldwide Palliative Care Alliance(WPACA) mapped out the global development of palliative care dividing countries into 4 categories. Category 1 where there is no known development of palliative care, category 2 where development is at the level of capacity building, category 3 where there is isolated provision of palliative care services and category 4 where services are approximating integration into mainstream medicine. Among these countries, only Singapore and Malaysia have achieved category 4 status while majority are in category 3 (Indonesia, Thailand, Philippines, Myanmar, Cambodia, Brunei and Vietnam). Regardless of the level of development, challenges faced in developing palliative care in Southeast Asia are common throughout and include first and foremost barriers of drug availability and fear of using opioids amongst public as well medical practitioners. Apart from this is the challenge of public perceptions towards death and dying which have made development of this discipline difficult. Even till today there are many misconceptions regarding the nature and concept of palliative care amongst healthcare professionals. For countries that are more advanced in their development, the key challenge is now how to continue development in a sustainable manner and how to improve and maintain standards of care. In Malaysia, palliative care began in the early 1990s with the development of voluntary organisations providing home-based services for patients nearing the end of their terminal cancer. In 1995 the concept was introduced into government hospitals and soon received nationwide support by the Ministry of Health in Malaysia. In 2005, the subspecialty of palliative medicine was established and a formalised training programme for medical specialists was developed. At present there are a total of 18 trained palliative medicine specialists in Malaysia. The country now has 2 more in training. A diploma programme for nurses, physiotherapists and occupational therapists was developed in the Ministry of Health which has now trained 38 nurses and paramedics who have now become permanent stakeholders in palliative care service provision and development. Apart from this, non-governmental organizations also serve to complement the services provided by the medical palliative care services in Malaysia and there are currently 25 services throughout the country providing homecare. It is with such initiatives that Malaysia hopes to create a sustainable and credible workforce to continue the development and growth of palliative care throughout the nation and possibly the region.

Keywords: palliative care, opioid availability, end-of-life care, advanced cancer

ED02.05 PALLIATIVE CARE IN IRAN

Reza Malayeri

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It is well known that palliative care is a necessity in cancer patients, as early on as the time of diagnosis. In adult oncology, there is evidence to suggest early specialist palliative care improves HRQOL, mood, treatment decision-making, health-care utilization, advanced care planning, patient satisfaction, and end-of-life care (1). Earlier admission to community-based palliative care also reduces the use of Emergency departments by cancer patients in the 90 days before death (2). Palliative care for cancer patients is rather new in Iran and has a history of less than 7 years. Here we give an overview on the status of palliative care in Iran. We also present the demographics of our patients in the first and largest palliative care ward in Iran over the last two years. Iran has a population of around 80 million people. In Iran, cancer is known as the third cause of death. Adult mortality rate of cancer in different regions of Iran is estimated 48-112 cases per million people among the females and 51-144 cases per million people among the males (3). Also, mortality rate related to cancer was about 53500 people in 2014 (4). The majority of cancer patients expire in the intensive care units (ICU), whereas bed occupancy of ICUs is in crises, being about 100% in Iran. For each ICU bed, 4 patients can be attended (5). We currently have around 8 active palliative care units for cancer patients and one palliative care ward in Iran, all run by charities. In these palliative care units, we have oncologists, palliative care specialists, pain specialists, psychologists, spiritual care specialists, social workers and dieticians. A total number of 3677 patients, ages between 16 and 94 (Median 61), of whom 3277 (89%) with a similar age distribution had a cancer diagnosis were referred to our palliative care unit in Firoozgar Hospital, which is run by the Ala Charity, in Tehran in the last three years. 1770 female (54%) and 1457 male (46%) advanced cancer patients were referred. A number of 389 (12%) patients had breast cancer,
339 (10%) had hematologic malignancies, 312 (10%) had esophageal or gastric cancer, 311 (10%) had colorectal cancer, 105 (3%) had a cancer of the CNS, 101 (3%) had lymphoma, 93 (3%) had renal cancer, 87 patients (3%) had ovarian cancer, 81 (2%) had lung cancer, 54 patients (2%) had prostate cancer and 50 (2%) had pancreatic cancer. The other 40% of the cancer patients had either less frequent cancers or their exact cancer site was not recorded. In most countries, the gap between death and specific therapies is considered as an indicator of the quality of physician services and more length of time will be a better indicator for physician services, while cancer patients in health system of Iran receive specific treatment and chemotherapy even to moment of death. To consider countless benefits of home care and the patients’ desire to receive services at home, if we can provide the conditions that at least 20% of end stage cancer patients receive home based palliative care, 1000 deaths will occur at home yearly, and 1000 ICU beds will be released for use for other patients with better prognosis for survival (5). For this reason, the Ala charity has also started free of charge home care services in Isfahan and Tehran. Iran, like many other countries, needs many more palliative care units as well as an expansion of home based palliative care services to advanced and very advanced cancer patients. As palliative medicine is not financially lucrative, charities play a major role in setting up, maintaining and expanding these units. References:


Keywords: Palliative medicine, cancer, Iran

SESSION ED03: GLOBAL TOBACCO CONTROL POLICIES: ADVANCES & CHALLENGES
MONDAY, DECEMBER 5, 2016 - 14:30-15:45

ED03.01 TOBACCO CONTROL IN THE MIDDLE EAST
Feras Hawari
The King Hussein Cancer Foundation, Amman/Jordan

Despite many countries signing and ratifying the Framework Convention on Tobacco Control (FCTC), the prevalence of tobacco continues to be on the rise in the Middle East. For example, in countries like Jordan and Tunisia, tobacco prevalence among males is close to 50% and in Jordan specifically it is estimated to increase to 88% over the next 5 years according to the World Health Organization (WHO). In 2008 it was estimated that five million people died due to tobacco related illnesses. This number is expected to increase to eight million in the year 2030 with individuals from low- and middle-income countries making up approximately 80% of these deaths. Tobacco is a risk factor for all major non-communicable diseases (NCDs) such as cardiovascular diseases, cancer, pulmonary diseases and diabetes mellitus. The developing countries and the Middle East in particular is bracing for at least a 25% increase in such diseases over the next few years. The world economic forum estimates that the cost for such chronic disabling diseases will exceed USD 15 trillion with cancer costs specifically reaching close to USD 3 trillion. The WHO outlined six strategies that, when implemented simultaneously, will result in significant reduction in tobacco prevalence and its related morbidity and mortality. Those strategies known as MPower (Monitor tobacco use and prevention policies, Protect people from tobacco smoke, Offer help to quit tobacco use, Warn about the dangers of tobacco, Enforce bans on tobacco advertising, promotion and sponsorship, Raise taxes on tobacco) when implemented in a country like Jordan, for example, close to 180,000 deaths can be prevented over 5 years. Despite the documented benefits of these six strategies, compliance with implementing them across the Middle East remains low. Only few countries have pictorial warnings, exposure to second hand smoke (SHS) is high, tobacco prices remain low and smoking cessation services are scarce. As the population in the Middle East age and with the ongoing rise in tobacco prevalence and obesity, cancer is expected to be on top of the list of diseases causing death and disability in the region. For that reason, King Hussein Cancer Center (KHCC), one of the leading cancer centers in the region, took on the challenge of fighting tobacco across the region in collaboration with regional and international partners. KHCC became the regional host for Global Bridges (an international TDT healthcare alliance co-founded by the Mayo Clinic, the American Cancer Society, and the University of Arizona). The main mission of this collaboration is to address the implementation of article 14 of the FCTC agreement and design and implement effective programmes to promote the cessation of tobacco use and provide adequate treatment for tobacco dependence (TDT). This will also serve to address one of the six strategies recommended by the WHO; Offer help to quit tobacco use. Tobacco dependence in the region is severe. The high number of cigarettes smoked per capita and the significant exposure to SHS make people less capable of quitting on their own. Aiding TDT across the region would respond to the high demand for such service (more than 65% of smokers are interested in quitting) and help curb the expected epidemic of NCDs. Long term, quitting tobacco generally reduces the risk of disease and premature death by 90% for those who quit before the age of 30 and by 50% for those who quit before the age of 50. In addition, TDT will optimize the management of certain NCDs such as cancer resulting in better treatment outcomes and long-term survivals. Over the past 5 years, KHCC developed partnership with countries across the Middle East and worked on training healthcare providers (HCPs) on how to treat tobacco dependence (figure 1). More than 2000 HCPS were trained to date (figure 2). Furthermore, 4 hubs designated for TDT training were established in Oman, Egypt, Tunisia and Morocco. In addition, an evidence-based TDT training curriculum specifically designed for the Middle East was developed and in the process of being made available in 3 languages; Arabic, English and French. In conclusion, tobacco dependence represents a major threat to the health and wellbeing of the people in the Middle East. Significant rise in NCDs including cancer is expected over the next few years. Many collaborative initiatives are underway to address this sever epidemic.

Keywords: Middle East, Training, tobacco, treatment

ED03: GLOBAL TOBACCO CONTROL STRATEGY: LESSONS LEARNED
Mike Daube
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This presentation will outline the developments that have led the international tobacco industry to describe Australia as “the darkest market in the world”. This will be presented in the context of international developments with implications and recommendations for other countries, businesses, and researchers, clinicians, health professionals, health organisations and governments. There will be discussion of the origins and early history of tobacco control in Australia; the components of comprehensive tobacco control programs; policy-relevant research; successes, failures and distractions; and the roles of key organisations and individuals. This will be followed by an outline of major developments, including the establishment of a consensus approach; national and local approaches; activity by key groups; progress across a range of key areas including public education, advocacy, tobacco advertising bans, taxation, health warnings, smoke-free, excluding tobacco indicators, with the tobacco industry’s contribution; cessation support; and other measures. There will be discussion of the Australian world-leading tobacco plain packaging legislation, which is now being replicated in many other countries, and the very encouraging resultant trends. The Australian experience and successes will be presented in a global context, with recognition that the tobacco industry will always oppose any measures that might reduce smoking and is constantly looking for new ways to resist action and promote its products. From this conclusions will be drawn and recommendations made for all concerned to reduce smoking, with consideration of next possible developments.

Keywords: Plain packaging, The world’s darkest market, Tobacco Control, advocacy

SESSION ED04: BRONCHOPULMONARY CARCINOID TUMORS
MONDAY, DECEMBER 5, 2016 - 14:30-15:45

ED04.01 SURGERY IN BRONCHOPULMONARY TYPICAL AND ATYPICAL CARCINOIDs

Pier Luigi Filosso1, Alberto Sandri2, Francesco Guerra3
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Complete surgical resection of the tumor is the treatment of choice for Bronchopulmonary Carcinoids (BCs). The goal is to resect the lesion, saving as much lung parenchyma as possible. The type of surgical approach and resection are strictly depend on: a) tumor’s location, b) tumor’s histology and c) presence of lymphnodal metastases. In case of peripheral small BC (Figure 1), the type of surgical resection (wide wedge resection vs segmentectomy or lobectomy) is still matter of debate. Few scientific evidences (1,2) report that a wedge resection could be safely proposed since, in multivariate analysis, long-term survival is not compromised when this approach is used. However, those studies are retrospective, sometimes with limited data on the patients’ follow-up and the number of wedge resections is limited: therefore it is very difficult to draw definitive conclusions with those potential biases. The statement that a wedge resection should be reserved to a small peripheral N0 Typical Carcinoid (TC) seems to be more prudent. An anatomical resection (segmentectomy/lobectomy) should be proposed in case of an Atypical Carcinoid (AC), or whenever the tumor can not be resected in a less invasive manner (e.g. centrotracheal lesion or when the lobe is totally occupied by the tumor – Figure 2.). The aim to preserve as much lung tissue as possible is the cause of the development of tissue-sparing surgical techniques (the so called “bronchial sleeve resections” and the “sleeve lobectomies”). The first contamination of the concept was a bronchial sleeve resection with the tumor, without any lung parenchyma excision; in the latter, a formal lobectomy with bronchoplastic procedure, is performed to avoid major pulmonary resections (e.g.: bilobectomy or pneumonectomy). An intraoperative frozen section of the bronchial margin has to be performed in all bronchoplastic procedures to confirm that no neoplastic cells are present in the operated area. A complete surgical resection is mandatory and the presence of lymph nodal metastases has been reported in several papers (7,8): those patients, in case of peripheral small BC (Figure 1), the type of surgical resection (wide wedge resection vs segmentectomy or lobectomy) should be proposed in case of peripheral small BC. However, those studies are retrospective, sometimes with limited data on the patients’ follow-up and the number of wedge resections is limited: therefore it is very difficult to draw definitive conclusions with those potential biases. The statement that a wedge resection should be reserved to a small peripheral N0 Typical Carcinoid (TC) seems to be more prudent. 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A complete surgical resection is mandatory and the presence of lymph nodal metastases has been reported in several papers (7,8): those patients, in case of peripheral small BC (Figure 1), the type of surgical resection (wide wedge resection vs segmentectomy or lobectomy) should be proposed in case of peripheral small BC. However, those studies are retrospective, sometimes with limited data on the patients’ follow-up and the number of wedge resections is limited: therefore it is very difficult to draw definitive conclusions with those potential biases. The statement that a wedge resection should be reserved to a small peripheral N0 Typical Carcinoid (TC) seems to be more prudent. An anatomical resection (segmentectomy/lobectomy) should be proposed in case of an Atypical Carcinoid (AC), or whenever the tumor can not be resected in a less invasive manner (e.g. centrotracheal lesion or when the lobe is totally occupied by the tumor – Figure 2.). The aim to preserve as much lung tissue as possible is the cause of the development of tissue-sparing surgical techniques (the so called “bronchial sleeve resections” and the “sleeve lobectomies”). The first contamination of the concept was a bronchial sleeve resection with the tumor, without any lung parenchyma excision; in the latter, a formal lobectomy with bronchoplastic procedure, is performed to avoid major pulmonary resections (e.g.: bilobectomy or pneumonectomy). An intraoperative frozen section of the bronchial margin has to be performed in all bronchoplastic procedures to confirm that no neoplastic cells are present in the operated area. A complete surgical resection is mandatory and the presence of lymph nodal metastases has been reported in several papers (7,8): those patients, in case of peripheral small BC (Figure 1), the type of surgical resection (wide wedge resection vs segmentectomy or lobectomy) should be proposed in case of peripheral small BC. 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SESSION ED05: THE 8TH EDITION OF THE TNM STAGING SYSTEM
MONDAY, DECEMBER 5, 2016 - 16:00-17:30

ED05.01 WHAT'S NEW IN LUNG CANCER STAGING?
Misao Azamura
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The tumor, node and metastasis (TNM) classification for malignant tumors has been periodically revised in the International Union for Cancer Control (UICC) and American Joint Committee on Cancer (AJCC). As for lung cancer, the process of revision is quite unique compared with malignancies of other organs in that the corresponding professional society, the International Association for the Study of Lung Cancer (IASLC), has been playing a principal role in database construction, making revision agenda, simulation, and validation as a proposal to UICC and AJCC. The agenda articles have been already published for T, N, M, and stage grouping in the official disease of IASLC. In brief, the IASLC database included 77,156 evaluable patients diagnosed with lung cancer from 1999 to 2010, originating from 35 different databases in 16 countries of 5 continents. Among these, the data of 3905 patients were given by electric data capturing. In the T descriptors, new tumor-size groupings were created: T1a (<1cm), T1b (1-2cm), T2a (2-3cm), T2b (>3cm), T2b (>4cm), T3-4.5cm, and T4 (>7cm). Endobronchial location <2cm from the carina has better prognosis than any other T3 descriptor and will be classified as T2. Total atelectasis/pneumonitis will be classified as T2 because it has a T2 prognosis. Diaphragmatic invasion will be T4. Visceral pleural invasion remains the same, and mediastinal pleura invasion, seldom used, disappears as a T descriptor. The N component remains the same, but extrathoracic metastases are divided into single extrathoracic metastasis (new M1b) and multiple extrathoracic metastases in a single or multiple organs (M1c). Regarding stages, stage IA is divided into IA1, IA2 and IA3 to accommodate T1a, T1b and T1NM0 tumors; all N1 disease are stage IIB, except for T3-T4N1M0 that are IIIA; a new stage IIIIC is created for T3-T4N3M0 tumors; and stage IV is divided into IVA (M1a and M1b) and IVB (M1c). The 8th edition of the TNM classification of lung cancer defines new tumor-size groups, confirms the prognostic relevance of quantifying nodal disease, establishes a new category for single extrathoracic metastasis, and creates new stage groupings. Looking at these, the importance of the accurate measurement of tumor diameter and accurate counting of the swollen nodes and lesions of distant disease has been raised. In this way it improves our understanding of the anatomic extent of the tumor, enhances our capacity to indicate prognosis at clinical and pathologic staging, and increases the possibilities of research by facilitating tumor stratification for future clinical trials.

Keywords: Prognosis, TNM classification, Staging, lung cancer

ED05.02 UPDATE ON THE MESOTHELIOMA STAGING SYSTEM
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The initial TNM staging classification for malignant pleural mesothelioma (MMP), published in the 6th edition of the UICC and AJCC staging manuals, was derived from analyses of small retrospective surgical series. It has been criticized for being insufficiently evidence-based and difficult to apply to clinical staging. To identify potential deficits in the MMP staging classification, the IASLC Staging and Prognostic Factors Committee (ISPC), in collaboration with members of the International Mesothelioma Interest Group (IMIG), initiated a large multinational database in 2009. This approach was modeled on methods used by the IASLC to revise the lung cancer staging system. Data were submitted on 5,101 patients from 15 centers on 4 continents, all of whom had some form of surgical management, and an initial analysis was published in 2012. Overall survival (OS) data largely supported continued use of the original MMP staging classification but identified several important areas for improvement, particularly for the T and N components. To address issues raised by this initial analysis, a second iteration of the IASLC MMP database was started in 2013 to inform revisions for the 8th edition of the AJCC/UICC staging systems. The data dictionary was revised to provide more granular information for the T, N and descriptors and a new electronic data capture (EDC), housed at the biostatistical center CRAB (Cancer Research and Biostatistics, Seattle, WA, USA), was developed. Additional investigators...
who could provide valid information on patients with tumors staged clinically and managed non-surgically were recruited. Data to inform revisions for the 8th edition of the MPM staging classification originated from 23 centers on 4 continents and included 3,519 cases of which 2,460 passed the initial eligibility screen. As planned, this dataset included both patients managed surgically and non-surgically. OS examined for T categories according to the current 7th edition staging classification showed a clear difference between all clinically staged categories except for T1a versus T1b and T3 versus T4. Pathological staging failed to demonstrate a survival difference between the adjacent categories with the exception of T3 versus T4. Performance improved with collapse of T1a and T1b into a single T1 category. Analyses suggested that all current T descriptors should be maintained. Tumor thickness and morphology were also significantly associated with OS. Consequently, a recommendation has been made that the clinical and pathological T1a and T1b into a T1 category. Because simple measurement of pleural thickness had prognostic significance, it was felt that this should be examined further with a view to incorporation into future revisions of the staging classification. With respect to the N categories (as defined in the 7th edition staging classification), there was no significant difference in OS cN0, cN1 and cN2, likely reflecting the inaccuracies of current methods for clinical lymph node staging in MPM. For pathologically staged tumors, patients with pN0 or pN2 tumors had a worse OS than those with pN2 tumors but no OS difference was noted between those with pN1 and pN2. Exploratory analyses found that tumors with both pN1 and pN2 nodal involvement had a poorer OS than those with pN2 alone. Consequently, a recommendation was made to collapse N1 and N2 into a new N1 category and to relabel the current N3 category as N2. Larger numbers of well-staged cases are needed to determine whether this new N1 category should be subdivided in the future according to the number of involved lymph node stations. Of the 3,519 submitted cases, 84 were cM1 at diagnosis. Median OS for cM1 was significantly worse than for T4 or N3 (as defined in the 7th edition) supporting inclusion of only cM1 in the stage IV group. Exploratory analyses suggested a possible difference in OS for single versus multiple site cM1 but additional data are needed in the future to determine the validity of this finding. Candidate stage groups were developed using a recursive partitioning and amalgamation (RPA) algorithm applied to all cM0 cases. Based on these analyses, optimal stage groupings proposed for the 8th edition of the staging classification were: stage IA (T1N0), stage IB (T2N0), stage II (T3N0), stage IIIA (T1N0M0), stage IIIB (T1N2M0 to T4 and stage IV (any M1)). These new stage groupings are substantially different from what is currently used in the 7th edition. The IASLC database is the largest available multinational database in this rare malignancy and has provided the first evidence-based revisions of the TNM classification for MPM leading to substantial changes in the T and N components and the stage groupings. Continued efforts to accrue to this database will be important to inform further changes for the 9th edition of the staging classification.1,7

Reference List


What’s New in Esophageal Cancer Staging? Thomas W. Rice, MD

What’s New in Esophageal Cancer Staging? Thomas W. Rice, MD The 8th edition cancer staging manuals will be published later this year, and the new staging recommendations will go into effect January 1, 2017. Staging of the esophagus and esophagogastric junction for the 8th edition of the AJCC/UICC manuals was developed on a strong 7th edition foundation. A greatly enhanced Worldwide Esophageal Cancer Collaboration (WECC) database, with a substantial increase in both numbers of patients (22,654) entered and variables (39) collected, permitted a more dynamic and dependable Random Forest-based machine learning analysis. Random Forest analyses provided risk-adjusted survival estimates for all patients, from which distinctive and homogeneous stage groups with monotonically decreasing survival were identified. Cancer Categories There were no major changes in cancer categories; however, there were some important refinements for T, N, grade, and location. Subcategorying of pT1 into pT1a and pT1b enhanced and improved Stage I grouping. Regional lymph nodes (N) were clarified in a new and simplified map. Undifferentiated cancers now require additional analyses to expose histopathologic cell type. If glandular origin can be determined, the cancer is staged as Grade 3 adenocarcinoma; if squamous origin can be determined or if the cancer remains undifferentiated after full analysis, it is staged as Grade 3 squamous cell carcinoma. Cancer location, not important for adenocarcinoma stage grouping, in conjunction with grade is necessary to subgroup only pT3N0M0 squamous cell carcinoma. The definition of the esophagogastric junction was revised; cancers involving the esophagogastric junction with epusters 2 cm or less into the gastric cardia are staged as adenocarcinomas of the esophagus, while those with more than 2 cm involvement are staged as stomach cancers. Stage Groupings Pathologic Stage Grouping (pTNM) Historically, pathologic staging after esophagectomy alone has been the sole basis for all cancer staging, regardless of classification (c, yc, yp, r, and a). Today, pathologic stage has lost some of its clinical relevance for advanced-stage cancer as neoadjuvant therapy replaces esophagectomy alone. However, it remains important for early-stage cancers and as a key reference point. Dissimilar stage group composition and survival profiles necessitated separate staging for adenocarcinoma and squamous cell carcinoma. Neoadjuvant Pathologic Stage Grouping (ypTNM) New to the 8th edition is stage grouping of patients with esophageal cancers who have had neoadjuvant therapy and pathologic review of the neoadjuvant specimen (ypTNM). Drivers of this addition include absence of equivalent pathologic (pTNM) categories for the peculiar neoadjuvant pathologic categories (ypT0N0-3M0 and ypTisN0-3M0), dissimilar stage group compositions, and markedly different survival profiles. Grade and location play no role in neoadjuvant pathologic stage grouping. These groupings are identical for both histopathologic cell types.

Stage Grouping (cTNM) Also new to the 8th edition is clinical stage grouping (cTNM) prior to treatment decision. Clinical staging is done typically in the absence of complete histologic cancer data, because clinical TNM categories are typically defined by imaging and examination of needle aspiration and biopsy specimens. Dissimilar stage group composition and survival profiles necessitated clinical stage grouping (cTNM) distinct from pathologic stage grouping (pTNM). There is separate clinical staging for adenocarcinoma and squamous cell carcinoma.

for clinical staging (CTNM) of cancer of the esophagus and esophageoplastic
junction for the 8th edition AJCC/UICC staging manuals. Dis Esophagus. In
press.

Keywords: AJCC, cTNM, pTNM, ypTNM

SESSION ED06: SYMPTOM MANAGEMENT IN LUNG CANCER
MONDAY, DECEMBER 5, 2016 - 16:00-17:30

ED06.02 PAIN MANAGEMENT
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Introduction: Pain is the most common symptom in cancer patients and it
is also the most common symptom in lung cancer patients. [1] The majority of
patients with lung cancer present with advanced stage of the disease
at diagnosis. Symptoms may result from local effects of the tumor, from
regional or distant spread or from distant effects not related to metastases-
paraneoplastic syndromes. Pain in these patients may be associated with
depression, fatigue [2] and may affect quality of life and patients’ performance
status. Early palliative care including pain management may increase their survival. [3] Pain can be classified by type of pain or according
to the origin of the pain. The location or origin of the pain determines the
type of pain, thoracic or extrathoracic. Pain: Pain is often multifactorial in
origin and needs to be addressed in each aspect. It can be acute or chronic.
Acute pain can be caused by hemorrhage into a tumor, bone pain secondary
to a pathological fracture, visceral pain, i.e., from acute intestinal obstruction
or perforation of a viscous. Its duration is limited and predictable. Chronic
pain is differentiated by its longevity. It is estimated that approximately 75%
of cancer patients live with chronic pain. [4] It must be approached with
dual aim: relieving the pain as well as preventing further recurrences of
pain. Pathophysiology of Pain: Physiological pain is termed nociceptive
due to the stimulation of the sensory nociceptors located in tissues with damage. They are somatic, visceral, neurogenic and neuropathic pains. [5] Neuropathic pain is associated with a loss of opioid receptors in sensory afferents and an increased release of glutamate in the dorsal horn. The resultant hyperexcitability causes spontaneous pain and hyperalgesia and allodynia in areas adjacent to the nerve damage. There are three main causes of pain in patients with advanced lung cancer. Skeletal metastases are present in 34%, Pancoast tumor 31%, chest wall disease 21%. [6] Principles of Pain Management: The World Health Organization analgesic ladder for cancer pain relief provides a stepwise approach to managing pain in cancer patients. [7] This ladder includes paracetamol or non-steroidal anti-inflammatory drugs, Step 2 - weak opioids, i.e. codeine. Step 3 - strong opioids, i.e. morphine. Non-opioid and adjuvant treatments can be added to steps 2 and 3. Different routes of the administration of analgesics and their side effects management will be described. Their advantages and disadvantages of each route of administration will be pointed out. The most used adjuvant treatment such as tricyclic antidepressants and anticonvulsants, corticosteroids, topical analgesics, treatments of nausea, constipation, etc., are an integral part of management. Interventional procedures help reduce the doses of analgesics and their side effects. [8] Special mention will be about skeletal metastases and bone targeted agents such as zoledronic acid and denosumab, which have shown ability to reduce the pain and analgesic consumption in lung cancer patients. [9] Complementary therapies which help to control pain will also be mentioned. i.e. Acupuncture, [10] psychological methods of care, etc. Conclusion: Active multidisciplinary approach is required to manage pain in patients with advanced lung cancer. Multifactorial pain is frequent and may require several different analgesics, along with general palliative care and even special interventional procedures. Patients with advanced lung cancer live longer as there are more treatment options. It is of utmost importance to preserve a good quality of life with a better performance status to enable them to receive now further available therapies. [1] Caraceni A, Portenoy RK. An international survey of cancer pain characteristics and syndromes. IASP Task Force on Cancer Pain. Pain. 1999;82 (32):263-74. [2] Laird BJ, Scott AC, Colvin LA, et al. Pain, depression, and fatigue as a symptom cluster in advanced cancer. J Pain Symptom Manage. 2011;42(1):1-11. [3] Temel JS, Greer JA, Muzikansky, A, et al. Early palliative care for patients with metastatic non-


Keywords: pain-pathophysiology and management, pathophysiology of pain, principles of pain management

ED06.04 BIOLOGY AND MANAGEMENT OF TUMOR CACHExIA
Jeffrey Crawford
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The International Consensus Conference definition of cancer cachexia is a multifactorial syndrome defined by an ongoing loss of skeletal muscle mass with or without fat mass that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment. As clinicians, we define cachexia clinically based on weight loss of 5% or greater or body mass index <20 kg/m², with 2% weight loss. On physical exam, we recognize cachexia based on gross loss of muscle mass and weakness, often associated with physical findings such as temporal wasting and early kyphosis. In these patients with physical stigmata of cachexia are a small subgroup of the total population. If one assesses objective measures of muscle mass, approximately half of patients with advanced lung cancer will have muscle wasting at diagnosis and 2/3 of patients will develop it during their treatment course. This muscle wasting occurring through anabolic pathways, occurs across all weight groups, including those with normal weight, overweight and obesity. These patients would not be recognized clinically to be cachetic. Yet, they have significant clinical consequences from muscle wasting. The use of standardized CT for the quantitative assessment of skeletal muscle mass and fat is an important tool that has helped us better understand the importance of muscle and its impact on cancer outcomes. Muscle wasting is associated with an increased risk of dose limiting chemotherapy toxicity, shorter time to disease progression and reduced overall survival. Clinically, the cancer patient with cachexia undergoes a progressive decline in muscle mass with associated weakness, fatigue and reduced quality of life. Patient reported outcomes include weakness, declining muscle strength, reduced mobility and impact on physical performance. At a molecular level, this loss of muscle mass is associated with a number of biochemical changes in enzymes, regulatory proteins, altered metabolic pathways, increased pro-inflammatory cytokines, and increased pro-inflammatory markers. The driving force for muscle wasting in cancer patients is the competition for nutrients between the cancer and the host often complicated by decreased protein/caloric intake. However, the mechanisms that both incite and promote the ongoing process of muscle loss are complex and include factors associated with direct muscle loss including the release of cytokines such as tumor necrosis alpha and interleukin 6, as well as myostatin and activin. One strategy that might ameliorate the cachexia process include therapeutic approaches that block these cytokine mediated pathways and several agents are in development. Another approach has been to try to increase muscle growth signals at baseline and during treatment such as selective androgen receptor modulators (SARM) and ghrelin mimetics. A first in class SARM, enobosarm has shown promising results with improvement of muscle mass and physical function in patients with cachexia. Subsequent phase III trials in patients with advanced lung cancer receiving chemotherapy have shown increase in muscle mass in the enobosarm treatment group versus placebo, but physical function testing using stair climb measurement were inconsistent. Meanwhile, trials of anamorelin, a ghrelin receptor agonist have also demonstrated improvement in skeletal muscle mass. In phase III trials in patients with advanced lung cancer and cachexia, improved appetite and weight gain. Again, functional improvement as measured by hand grip strength was not observed. It is not clear why there is a lack of association of these promising agents that increase muscle mass, with functional improvement. This may reflect issues regarding just the patient population, the objective test being used, the duration of treatment or other factors. However, these phase III trials in advanced lung cancer represent an important step forward in our understanding of cachexia and possible therapeutic interventions. Currently, as we are moving forward with the development of new agents for cachexia, it is important for us to recognize the magnitude of the problem in our patients. Until CT imaging becomes a standard clinical technique for assessment of muscle mass, we need to rely on our standard clinical approaches of history and physical exam. Perhaps most importantly, is our documentation of the degree of weight loss in our patients as a routine measure at baseline and during treatment. As we assess other patient reported outcomes such as pain, fatigue and functional status. Incorporating weight loss along with body mass index can be a very powerful tool for predicting outcome and survival for our patients.

Keywords: Cachexia, muscle wasting, sarcopenia

ED06: SYMPTOM MANAGEMENT IN LUNG CANCER
MONDAY, DECEMBER 5, 2016 - 16:00-17:30

ED06.06 DECISIONS IN CASE OF INTRACTABLE SYMPTOMS
Jean Klastersky1, Bénédicte Michel1, Isabelle Libert1, Aspasia Georgala2, Myriam Obiols1, Florence Lewis1, Dominique Lossignol1
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Case report: A 55-year-old lady was diagnosed with small cell lung cancer in late 2008. She had been a long-time cigarette smoker without, any other significant medical history. She was a housewife, deeply religious and dedicated mother to 2 children. As a first treatment for her cancer, she received radiotherapy on the right apex and mediastinum, concomitantly with chemotherapy (cisplatin plus etoposide), early in 2009. Six months later, she presented a very painful right shoulder and chest wall. Chemotherapy was resumed, with some improvement of the pain, but late in 2009, radiotherapy had to be administered to the chest for uncontrolled pain; oral etoposide was given without much benefit. The pain progressively increased and the patient was complaining of increasing shortness of breath. As the tumour was clearly progressing, in 2010, with further lung, bone and liver involvement, a decision was made to discontinue any specific oncological treatment. Both symptoms pain and dyspnea increased in intensity and became uncontrolable late in 2010; the patient and her family requested sedation at any cost. The patient was started on palliative sedation and died peacefully after 2 days, with her family at her side.

Discussion In case of dyspnea due to lung cancer progression, corticosteroids, morphine and oxygen are used since many years; novel options were introduced timidly during the last years. These new options include non-invasive ventilation, high-flow oxygen and rational use of medications usually prohibited in patients with respiratory distress, such as benzodiazepines, antidepressants and synthetic opioids [1]. The World Health Organization (WHO) scale for cancer-related pain proves to be an effective approach to pain management in cancer patients [2], and many variations based on it have been proposed [3]. However, these approaches represent pragmatic and empiric attitudes that are rarely evaluated in prospective studies. There is also a lack of consensus about the use of co-analgesia and other supportive approaches for refractory pain [5], although pragmatic recommendations exist, a comprehensive algorithm for the management of refractory pain is still lacking. Based on the experience in our supportive care unit, we proposed a comprehensive model for the progressive management of pain in cancer patients (Figure 1). Finally, the approach to pain (or other symptoms) that is beyond medical control, fortunately a relatively rare situation, has not been clearly defined [6,7]. Palliative sedation or euthanasia is always an emotionally and ethically challenging event for all involved and implies to meet the needs of the patient and family but also those of the caregivers [8, 9, 10] and requires repeated and professional counselling with the patient and family as well as regular debriefing sessions with the medical and nursing teams. Although the decision to offer and provide palliative sedation or euthanasia (if requested by the patient and not illegal) is never easy, it should be seen, however, as the medical duty to safeguard the patient’s autonomy, the principle of individual freedom to make choices.

(See Figure next page)
SESSION ED07: CLASSIFICATION AND DRUGGABLE TARGETS OF THORACIC TUMORS
TUESDAY, DECEMBER 6, 2016 - 11:00-12:30

ED07.02 THE 2015 WHO CLASSIFICATION OF NEUROENDOCRINE TUMORS
Elisabeth Brambilla
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France Neuroendocrine lung tumors were considered as separate entities in the previous WHO classification 2004: the carcinoid tumors, small cell lung carcinoma (SCLC) and large cell neuroendocrine carcinoma (LCNEC) were grouped separately. However, in the current WHO 2015 classification, they are grouped together. They are listed in the order of their frequency with SCLC first as it is the most common. SCLC (15% of lung tumors) is a malignant epithelial tumor which consist of densely packed small cells with scant cytoplasm, finely dispersed granular chromatin and absent or inconstant nucleoli. In contrast LCNEC is made of large cells and should show both neuroendocrine morphology (rosettes, palisades) and immunohistochemical neuroendocrine markers (at least one). Both SCLC and LCNEC can be pure or combined with NSCLC components but keep their diagnostic priority (SCLC– or LCNEC–combined). Carcinoid tumors are neuroendocrine malignancies accounting for <1% of all lung cancer, divided in two categories with highly different frequencies, the typical and atypical carcinoids, the last being less frequent. Carcinoid tumors are neuroendocrine malignancies with a high quality H&E stained section and in well preserved cytological samples, immunohistochemistry (IHC)/neuroendocrine markers can be very helpful in diagnosing pulmonary NE tumors especially in small biopsies or fragmented/ crushed artefact. Endocrine morphology and neuroendocrine IH markers are both required for the diagnosis of LCNEC. The cases with one missing (endocrine morphology or NE markers) are considered as large cell carcinoma in the absence of other differentiation marker on resection specimens, and as non-small cell lung carcinoma on small samples (cytology or biopsy). Mitotic counts are still retained to differentiate typical carcinoids (less than 2 mitoses per mm²) from atypical carcinoids (2 to 10 per mm²) and from high grade NE tumors SCLC and LCNEC (more than 11 mitoses per mm²), for being more reproducible than KI-67 evaluation. The role of Ki-67 is mainly to separate the high grade SCLC and LCNEC (more than 40%) from the carcinoid tumors (from 1 to 15%) especially in small biopsies with crushed/ or necrotic tumor cells. It is recommended to avoid the diagnosis of SCLC or LCNEC for tumors with less than 50% and 40% MIB1/KI67 index respectively. Data are conflicting regarding the use of KI-67 in separating typical from atypical carcinoid tumors, so it is not recommended in this setting. Careful counting of mitoses is essential as it is the most important histologic criteria for separating typical from atypical carcinoid and the carcinoids from the high grade SCLC and LCNEC. Due to recognition of the potential overlap in the morphology of LCNEC and basaloïd squamous cell carcinoma, it can be helpful to confirm negative squamous markers (i.e. p40) in TTF-1 positive tumors that otherwise meet criteria for LCNEC. Many recent progress have been made on the comprehensive genomic profiles of SCLC (1, 4), LCNEC and carcinoids (5). Although sharing NE features, these tumors group substantial and significant differences. Recent comprehensive genomic analysis have established the genomic profile of SCLC (3, 6). Their unique and remarkable characteristic is the universal bi-allelic alteration of both TP53 and RB1 gene (100% for TP53 and 93% for RB1) by different alterations of each of the 4 alleles: non synonymous mutations, damaging mutations by complex genomic rearrangements. Locally clustered mutations, indicative of functionally selected, occurred on CREBBP (15%) and EP300 (13%) genes, inactivating their histone acetylase functions. Notch family genes inactivating their protein functions occurred in 25% of SCLC (7). Notch is considered as a master regulator of NE differentiation. LCNEC genomics share characteristic features with SCLC for a part of LCNEC (SCLC-like LCNEC) or with AD /SQC for another part (about 25%). Mutations pattern and frequency of combined cases imply a considerable plasticity of these tumors which might represent an evolutionary trunk branching SCLC to NSCLC. Carcinoid is a unique example of a tumor driven entirely by chromatin modifiers and remodeling genes, which are absent in SCLC. In summary, 51% of carcinoid carried mutations in chromatin remodeling genes. In addition, the eukaryotic translation initiation factor (EIF4AX) was mutated in 9% of cases, genes of the E3 ubiquitin ligases system were mutated or rearranged in 18%. Altogether 73% of carcinoids have driver genes that are candidates for targeted therapy. New evidence is provided that carcinoid is not an early progenitor of high grade NE tumors, SCLC and LCNEC. References: 1. Travis WD, Brambilla E, Burke A, Marx A, Nicholson A. WHO Classification of the Tumors of the Lung, Pleura, Thymus and Heart. 4th Edition. Lyon: IARC Press; 2015. 2. Clinical Lung Cancer Genome Project (CLCGP), Network Genomic Medicine (NGM): A genomics-based classification of human lung cancers. Sci Transl Med. 2013;5(209):209ra513. doi:10.1126/scitranslmed.3006802. 3. Peifer M, Fernández-Cuesta L, Sos ML, et al. Integrative genome analyses identify key somatic driver mutations of small-cell lung cancer. Nat Genet. 2012;44(10):1041-1100. doi:10.1038/ng.2396. 4. Jeffe D, Jhang J, Chen M, et al. Comprehensive characterization of human lung cancer. Nature. 2015;524(7563):47-53. doi:10.1038/nature14664. 5. Fernández-Cuesta L, Peifer M, George J, et al. Genomic Characterization of...
SESSION ED08: EARLY-STAGE NSCLC: STATE-OF-THE-ART TREATMENT AND PERSPECTIVES
TUESDAY, DECEMBER 6, 2016 - 14:30-15:45

ED08.01 SURGERY OF EARLY STAGE NSCLC

Michael Mueller
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General considerations: Early stage lung cancer - a term in transition Generally early stage lung cancer is understood as stage I and stage II non-small lung cancer. An alternative understanding of early stage lung cancer is resectable disease. However, both definitions are imprecise and subject to development and expertise. Early stage lung cancer is resectable disease, which depends on regional philosophies and local expertise and therefore is the most unreliable and variable definition. The term resectability focuses on the T factor of the tumour and describes the ability of the surgeon to achieve radical resection. In contrast operability includes any potential regional and systemic spread and focuses more on the N and M descriptors. 2. Defining early stage lung cancer based on mediastinal node involvement Negatively, that single station N2 (N2a) is associated with the same five-year systemic spread and focuses more on the N and M descriptors. 2. Defining early stage lung cancer is understood as stage I and stage II non-small lung cancer was used. Preoperative staging: Of about 35%. However, for this presentation the current definition of resectability is a reported 92%. Even nodal negativeT3 tumours are associated with a survival benefit by complete mediastinal lymphadenectomy in patients with early stage lung cancer, but the results should not be generalized to patients staged only radiographically or those with higher stage tumours. The recommendation from this study is that a formal mediastinal en-bloc dissection may still affect survival and certainly optimally stages patients. In the subgroup analysis no difference between VATS and open lobectomy was observed for number of lymph nodes harvested and regarding long-term survival. 3 As minimally invasive surgery along with unilateral mediastinal lymphadenectomy generally prolongs operation times and the requirement ofưới lung ventilation for the elderly patients should be questioned and discussed individually. An alternative to thoracoscopic unilateral lymphadenectomy is offered by video-assisted mediastinal lymphadenectomy through the neck (VAMLA). The approach is similar to transcervical mediastinoscopy and allows for a radical b) dissection of all mediastinal lymph node stations. Besides the benefit of bilateral lung ventilation during this phase of the operation a bilateral mediastinal lymphadenectomy offers improved surgical radicality. Alternatives to surgical resection and the role of primary radiotherapy: In patients unfit for surgery SABR is the treatment of choice for peripherally located stage I non-small cell lung cancer. If SABR is not available a hypofractionated radiotherapy is advocated. A systematic Review comparing outcomes of SABR in patient SABR and surgery in patients with severe COPD revealed a higher 30 day mortality following surgery but similar overall survival at one and three years. 4 In a meta-analysis of 19 out of 318 papers with the best evidence addressing a comparison of SABR and surgical wedge resection both methods proved as reasonable alternatives to lobectomy in high risk surgical patients. In this analysis SABR was associated with reduced local recurrence compared to wedge resection and should be considered when wedge resection is planned due to anatomical location and size of the primary tumour in a patient who is high risk for surgery. 5 Although local tumour control may be comparable or even superior to extra-anatomic surgical resection a quite high rate of late radiological changes after stereotactic ablative radiotherapy for early stage lung cancer has to be considered. At one year follow-up the predicted probability of having expected or pronounced radiological changes after SABR were 65 and 22%. These changes included phenomena like mass-like appearance, radiation fibrosis, and rib fractures, which sometimes are difficult to differentiate from tumour recurrence. Summary: The ACCP guidelines address the question, who had to be considered a high risk candidate for surgery. With the advent of minimally invasive resection, the criteria to classify a patient as too ill to undergo anatomic lung resection are being redefined. Surgery remains the primary and preferred approach to the treatment of stage I and II NSCLC in patients with good or low surgical risk. Primary radiation therapy remains the primary curative intent approach to the treatment of stage I and II NSCLC in patients who refuse surgical resection or are determined by a multidisciplinary team to be inoperable. References: 1. Revised ESTS guidelines for preoperative mediastinal nodal staging for non-small-cell lung cancer. De Leyn P, Dooms C, Kuzdzal J, Lardinois D, Passlick B, Rami-Porta R, Turna A, Van Schil P, Venuta F, Waller D, Weder W, Zielinski M. Eur J Cardiothorac Surg. 2014 May;45(5):787-98. 2. Randomized trial of lobectomy versus limited resection for T1NO non-small cell lung cancer. Lung Cancer Study Group. Ginsberg RJ, Rubinstein LV. Ann Thorac Surg. 1995;50(3):615-22; discussion 622-3. 3. Tsutani Y, Miyata Y, Nakayama H, et al. Oncologic outcomes of segmentectomy...

ED08.02 THE ROLE OF RADIOThERAPY IN EARLY STAGE NSCLC

Suresh Senan

Radiation Oncology, VU University Medical Center, Amsterdam/Netherlands

Radiotherapy is a curative treatment for early-stage NSCLC. Following hypofractionated radiotherapy in 15 daily fractions of 4 Gy to biopsy-proven tumors, a prospective multicenter study reported a 3-year local control rate of 82.7% (95% CI: 69.7% to 90.5%). In the past decade, stereotactic ablative radiotherapy (SABR or SBRT) has become established as the guideline-recommended standard of care for medically inoperable patients with a peripheral early-stage NSCLC, as 5-year local control rates of 90% have been reported (Louie AV, 2015). SABR is usually delivered in 3-5 fractions, utilizes small margins for positional uncertainty, 4-dimensional computed tomography (4DCT) for treatment planning, multiple conformal beams or arcs for delivery, and cone-beam CT scans for daily setup. Where facilities for SABR are unavailable, hypofractionated radiotherapy delivered using 4DCT planning remains an acceptable curative treatment. Diagnosis Population studies reveal that a significant proportion of elderly patients, as well as those with severe co-morbidities, do not receive any treatment. Guidelines recommend that a tissue diagnosis be obtained before initiating treatment for early-stage NSCLC, but also permit the use of SABR following review by an expert tumor board, in tumors where the calculated probability of malignancy is high [Vansteenkiste, 2014; Callister ME, 2015]. However, any decision to proceed to a FDG-PET directed SABR approach in less fit patients requires a prospective multicenter study. The role of SABR in fit patients remains a topic of active debate. Indirect comparisons of outcomes following the two modalities have revealed conflicting results. The role of SABR in surgical patients is currently being investigated in 3 prospective randomized studies (NCT02468024, NCT02629458, NCT01753414), with a fourth study (VALOR) scheduled to open shortly.

Keywords: stereotactic radiotherapy, Early-stage lung cancer, follow-up,
toxicity

ED08.03 ADJUVANT CHEMOTHERAPY OF COMPLETELY RESECTED NSCLC

Glenwood Goss

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Adjuvant Chemotherapy of Completely Resected NSCLC Glenwood Goss Lung cancer remains the leading cause of cancer death worldwide and accounts for approximately 28% of all cancer deaths (1,2). Surgical resection is the cornerstone of therapy for early-stage disease, but relapse is high with 30-60% of patients with resected NSCLC still dying of their disease. Despite the results of a 1995 meta-analysis demonstrating a non-significant 5% survival advantage at five years with the addition of adjuvant cisplatin-based chemotherapy, no large randomized studies conclusively demonstrated a benefit following resection until 2003(3). Five large randomized trials were undertaken to determine if adjuvant platinum-based chemotherapy after curative surgery for NSCLC conferred a survival advantage. ALPI; IALT; IB10; CALGB 9633; and ANITA (4,5,6,7,8). Three of these five trials showed statistically significant improvements in overall survival, ranging from 4% (IALT) to 15% (IB10) at 5 years, corresponding to an absolute improvement in relapse-free survival from 4% to 61%. Of the two trials that did not demonstrate improved survival, one (ALPI) suffered from poor compliance to the treatment regimen (69%), and the second was a smaller trial (n=344) limited to patients with stage IB disease (CALGB 9633), which was likely underpowered to detect a statistically significant improvement in overall survival. Interestingly, despite being limited to patients with stage IB disease, CALGB 9633 did demonstrate an overall survival hazard ratio comparable to the other adjuvant trials (HR=0.8) that included patients with more advanced disease, despite not achieving statistical significance. Since the publication of...
original adjuvant chemotherapy trials, a number of meta-analyses have confirmed the benefit of adjuvant platinum-based chemotherapy after surgical resection for NSCLC(3,10). In these meta-analyses, all-stage (IIA-III) hazard ratios were in the range of HR=0.86, corresponding to an absolute benefit for chemotherapy on overall survival of 4-5% at 5 years. The benefit, however, was demonstrated to be stage dependent (albeit using older staging criteria versions), with the benefit only reaching statistical significance for stages II and III. While the role of adjuvant chemotherapy in stage I disease is controversial, comparable survival benefits in a high-risk group of patients with stage IB disease (tumors ≤4cm) suggests that there may be an overall survival advantage with adjuvant chemotherapy in this subgroup of patients, comparable to those observed in stage II and III disease (Strasas 2008). In 2009 the long term follow up of the IALT study (with a median follow up of 7.5 years) was reported. Results showed a beneficial effect of adjuvant chemotherapy on overall survival (hazard ratio [HR], 0.91; 95% CI, 0.81 to 1.02; P = .10) and on disease-free survival (HR, 0.88; 95% CI, 0.78 to 0.98; P = .02). However, there was a significant difference between the results of overall survival before and after 5 years of follow-up (HR, 0.86; 95% CI, 0.76 to 0.97; P = .01; HR, 1.45; 95% CI, 1.02 to 2.07; P = .04) with P = .006 for interaction. Similar results were observed for disease-free survival. The analysis of non-lung cancer deaths for the whole period showed an HR of 1.34 (95% CI, 0.99 to 1.81; P = .06) suggesting that those patients receiving adjuvant chemotherapy had a higher death rate from non-lung causes after 5 years(12). However these conclusions were not supported to be a difference in outcome between cisplatin doublet regimens. A median follow-up was 9.3 years (range, 5.8 to 13.8). Adjuvant chemotherapy continued to show a benefit (hazard ratio [HR], 0.78; 95% CI, 0.61 to 0.99; P = .04). There was a trend for interaction with disease stage (P = .09; HR for stage I, 0.68; 95% CI, 0.46 to 1.00; P = .02; stage II, HR, 0.92; 95% CI, 0.77 to 1.10; P = .87). Adjuvant chemotherapy resulted in significantly prolonged disease specific survival (HR, 0.73; 95% CI, 0.55 to 0.97; P = .03). Observation was associated with significantly higher risk of death from lung cancer (P = .02), with no differences in rates of death from other causes or secondary primary malignancies in the arms. They concluded that prolonged benefit of patients from the JBR.10 trial continues to show a survival benefit for adjuvant chemotherapy(13). Recently in a post hoc analysis of ECOG 1505, a comparison of adjuvant chemotherapy + bevacizumab for early stage NSCLC, Wakelee and colleagues had the opportunity to compare four different cisplatin doublet regimens. Of note, cisplatin in combination with doxetaxel, gemcitabine or pemetrexed. Median follow-up time for each chemotherapy doublet was: vinorelbine 54.3 months; docetaxel 60.3 months; gemcitabine 57.0 months; and pemetrexed 46.0 months respectively. The arms were well balanced for the major prognostic factors apart from smoking where the percentage of former smokers was slightly lower in the pemetrexed arm. There was no difference in the median number of cycles between arms. Both in the nonsquamous and squamous subgroups there was no difference in overall survival (nonsquamous logrank p=0.18 and squamous p=0.99) and disease free survival (nonsquamous p=0.54 and p=0.83). The authors concluded that there did not appear to be a difference in outcome between cisplatin doublet regimens(14). Despite the established benefit of adjuvant chemotherapy after curative surgery for NSCLC there is still much to be done with approximately 50% of patients still dying from disease. Furthermore, not all patients with early stage NSCLC are willing to proceed to chemotherapy in order to complete surgical resection (Booth 2010). As such, the long-term prognosis of patients with NSCLC, even among those with early stage disease, remains poor. Therefore it is imperative that we find new and better therapies to improve upon the results of surgical resection and adjuvant chemotherapy. Recent Oncologist Cancers. Cancer Research. Cancer Society. Cancer Statistics 2007. CA Cancer J Clin 2007; 57: 43-66. 3. L. A. Stewart, S. Burdett, J. F. Tierney, J. 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J Clin Oncol 2010; 28: 3427-8. Keywords: adjuvant chemotherapy, early stage non small cell lung cancer.
agent. (Table 1) Globally most targeted therapy adjuvant trials are being conducted in Asia, particularly China and Japan. ADJUVANT (C-TONG 1104) trial in China and IMPACT WJ066410L in Japan are phase III trials for patients with resected stage IIA-IIIA NSCLC comparing gefitinib to cisplatin/vinorelbine using DFS as the primary endpoint. (Table 1) Other trials outlined in Table 1 are exploring variations on this theme using gefitinib or cetuximab and either after or instead of adjuvant chemotherapy. The PD-1 inhibitors nivolumab and pembrolizumab are approved for the second line treatment of advanced NSCLC and will likely be utilized in first line in the near future. Based on their promise in advanced stage NSCLC, multiple trials with PD-1 and PD-L1 agents are ongoing. Most studies are for patients who have completed adjuvant chemotherapy (though some allow chemotherapy naïve patients) and they predominantly randomize patients to approximately 1 year of PD-1 or PD-L1 inhibitor therapy. Most include testing for PD-L1 expression, but do not exclude patients with low tumor levels of PD-L1. Many are placebo controlled. (Table 1) Chemotherapy has helped improve outcomes but continued investigations with novel approaches will be necessary to continue to improve cure rates for patients with resected early stage NSCLC.

The use of molecularly targeted agents for patients with tumors containing EGF/R or ALK translocations are promising with validation studies ongoing and the hope of immunotherapy is being investigated as well in multiple global trials. Table 1. Ongoing Phase III Targeted and Immunotherapy Adjuvant Trials

<table>
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<tr>
<th>Trial</th>
<th>Description</th>
<th>Primary Endpoint(s)</th>
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<tr>
<td>C-TONG 1104 NCT01450579</td>
<td>*Gefitinib vs. cisplatin/vinorelbine</td>
<td>3-year DFS</td>
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<tr>
<td>GASTO1002 NCT01996098</td>
<td>*Chemotherapy vs obs</td>
<td>5-year DFS</td>
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<tr>
<td>BD-IC-VS9 NCT2215240</td>
<td>*Chemotherapy vs placebo</td>
<td>2-year DFS</td>
</tr>
<tr>
<td>WJ066410L IMPACT</td>
<td>*Gefitinib vs. cisplatin/vinorelbine</td>
<td>5-year DFS</td>
</tr>
<tr>
<td>ALCHEMIST A081105/E4512</td>
<td>* Erlotinib vs placebo: ALK^ crizotinib vs placebo</td>
<td>OS</td>
</tr>
<tr>
<td>ALCHEMIST/ANVIL</td>
<td>*Erlotinib vs cisplatin: wildtype; US NCI NCTV, Nivolumab vs obs</td>
<td>OS/DFS</td>
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<tr>
<td>Impower010</td>
<td>Restricted to PD-L1^ Global, Atezolizumab vs placebo</td>
<td>DFS</td>
</tr>
<tr>
<td>MEDIA/36</td>
<td>aGlobal, MEDIA/36 vs placebo</td>
<td>DFS</td>
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<tr>
<td>Keynote-091</td>
<td>aETOP/EORTC, Pembrolizumab vs placebo</td>
<td>DFS</td>
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SESSION ED10: LOCALLY ADVANCED NSCLC: STATE-OF-THE-ART TREATMENT TUESDAY, DECEMBER 6, 2016 - 16:00-17:30

ED10.02 THE ROLE OF SURGERY IN STAGE III NSCLC

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Stage III non-small cell lung cancer (NSCLC) is a heterogeneous disease characterized by either locally advanced tumor infiltration and/or mediastinal lymph node involvement. Due to improvements in chemo-(CT)- and combined chemoradiation (CRT) therapy protocols, patients with locally advanced stage III NSCLC become potential candidates for curative resection more frequently. According to the TNM-7 classification, stage III NSCLC can be defined by the following 1 and N subsets: stage IIA: T3 N1-2, T4 N0-1; T1-2 N2; stage IIB: T4 N2, T1-4 N3. Five-year survival of stage III is generally around 25% taken all different therapy strategies together. Several studies have shown that induction treatment before surgery is beneficial in resectable cases and selected patients undergoing radical resection may have encouraging 5-year survival rates up to 60%. However, to date, no worldwide consent exists on the general role of surgery in curative attempt. Furthermore, it is still unclear if resectable patients might have greater benefit from induction CT compared to combined induction CRT and if concomitant CRT should be preferred over a sequential treatment. Only a small number of prospective phase II/III trials are available addressing these issues. A phase III trial comparing induction CRT plus surgery (S) with definitive CRT in patients with stage IIA/N2 published in 2009 has questioned the role of surgery since there was no difference in overall survival (OS) between the two groups [1]. However, the 30-day mortality was unacceptable high (26%) in the subgroup of patients undergoing pneumonectomy and thus patients with CRT and lobectomy had significantly improved survival compared to those with CRT alone. Moreover, several other retrospective series have reported encouraging long-term survival in selected patients undergoing induction treatment followed by surgical resection. The benefit of adding sequential RT to CT prior to surgery (S) in stage IIA/N2 has been investigated in a recent phase III randomised trial [2]. Patients underwent a non-surgical resection after median OS of 37 months compared to 26 months CT/S. Both groups had similar disease free survival (DFS) and it was concluded that RT did not add any benefit to induction CT prior to surgery. However, those with CT/S had an objective response, pathological complete response, a R0 resection rate and a more frequent downstaging compared to their corresponding comparison group which did not undergo surgery beforehand. The question of whether to apply RT concomitantly or sequentially to CT has been investigated in a recent meta-analysis [3]. Pooled data from six prospective trials suggested that concomitant CRT, as compared with sequential CT, improved survival of patients with locally advanced NSCLC, primarily because of a better locoregional control. However, these patients were treated without surgery and caution should be taken when transferring these conclusions to the neoadjuvant setting before surgery. From the surgical point of view, patients with local tumor invasion (T3-4 N0-1) including Pancoast tumors should be treated in multidisciplinary team with standard technical principles than those with mediastinal lymph node involvement (N2). In patients with T3 tumors invading the chest wall, diaphragm, mediastinal pleura, phrenic nerve or parietal pericardium and N1 involvement, primary resection can be undertaken. Induction therapy may improve local control rates in larger tumors even in patients not being candidates for surgery. In patients with single or two level N2 disease with good response after induction treatment, nodal downstaging and/or bulky N2 disease, surgery should be avoided due to the expected poor outcome. However, it has been well shown that patients in good performance status with single or two level N2 disease with good response after induction therapy may have improved OS when undergoing curative resection [7, 8]. On the other hand, patients with persistent N2 disease after induction treatment tend to have worse OS and high recurrence rates and thus should not undergo surgery. This finding strengthens the impact of invasive re-staging after induction treatment as proposed by recent staging guidelines. In conclusion, selected patients with stage III NSCLC may have beneficial outcome after surgery combined with CT or CRT. However, this holds true only for cases with response to induction treatment, nodal downstaging and when R0 resection is deemed achievable. Surgery should be avoided in patients with multilevel/bulky N2 disease or persistent mediastinal LN after induction treatment due to the expected poor outcome. The optimal sequence and modality of induction treatment has not been established in large prospective trials. References: [1] Alibas K, Swann RS, Rusch WV, Turrisi AT, Shepherd FA, Smith C, et al. Radiotherapy plus chemotherapy with or...

ED10.03 NEW DEVELOPMENTS IN RADIOTHERAPY OF STAGE III NSCLC

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NSCLC accounts for 80-85% of all lung cancers, and stage III disease constitutes about 40% of the total cases. The main treatment modality in these patients is radiotherapy, usually combined with concurrent chemotherapy. Five-year overall survival in stage III disease is merely 10-15%. Radiotherapy of thoracic tumors poses several challenges, such as tissue heterogeneity, tumor and organ motion and changing anatomy over the treatment course. Main approaches addressing these problems include dose intensification, altered fractionation and advanced radiation therapy techniques. Until recently, dose escalation was considered the main means to increase radiotherapy efficacy. Despite encouraging results of phase I-II studies, the results of recent RTOG trial 0617 were disappointing (1). This study compared high-dose radiotherapy (74 Gy/37 fractions) to a standard-dose (60 Gy/30 fractions) concurrently with weekly paclitaxel/carboplatin, with or without cetuximab. Surprisingly, median overall survival in the high-dose arm was significantly shorter (24 months vs. 29 months in the standard-dose arms; p=0.004) (1). It was speculated that the inefficacy of high-dose radiotherapy could be due to long overall treatment time and accelerated tumor repopulation. Shortening treatment time may be accomplished by accelerated radiotherapy. A phase III study investigating continuous hyperfractionated accelerated radiotherapy (CHART; 54 Gy/36 fractions of 1.5 Gy delivered 3 times daily over 12 consecutive days) showed increased efficacy compared to conventional fractionation (2). A CHARTWEL study, using the same fractionation but with weekend breaks, was not superior to conventional fractionation (3). A meta-analysis of 10 trials of accelerated or hyperfractionated radiotherapy in non-small-cell lung cancer (NSCLC). Radiother Oncol 2011;100:76-85. 4. Mauguen A, Le Pe’choux C, Saunders MJ, et al. Hyperfractionated or accelerated radiotherapy in lung cancer: an individual patient data meta-analysis. J Clin Oncol 2012;30:2788-97. 5. Chang YJ, Dong L, Liu H, et al. Image-guided radiotherapy for non-squamous cell lung cancer (NSCLC). Cochrane Database Syst Rev 2016;9:CD011505. 6. Sonke JJ, Balberbo J. Adaptive radiotherapy for lung cancer. Semin Radiat Oncol 2010;20:94-106. 7. Bezjak A, Rumble RB, Rodrigues G, et al. Intensity-modulated radiotherapy in the treatment of lung cancer. Clin Oncol 2012;24:508-20. 8. De Ruyscher D, van Baardwijk A, Steeves J, et al. Individualised isotropic accelerated radiotherapy and chemotherapy have been associated with improved long term survival of patients in stage III NSCLC: a prospective population-based study. Radiat Oncol 2010;120:228-233. 9. ZX Liao, JF Lee, R Komaki, et al. Bayesian randomized trial comparing intensity-modulated radiotherapy versus conventional radiotherapy for locally advanced non-small-cell lung cancer. J Clin Oncol 2016;34:135-40. 10. Dzidziszusko R, Jassem J. Randomized clinical trials using new technologies in radiation oncology: ethical dilemma for medicine and science. J Thor Oncol 2007;3:7-8.

ED10.04 NEW DEVELOPMENTS FOR SYSTEMATIC THERAPIES IN STAGE III NSCLC

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Concomitant chemoradiotherapy is currently the most widely accepted standard of care for patients with locoregionally advanced NSCLC. Induction chemotherapy represents an evidence-based alternative and is a particular attractive prior to surgery in patients with marginally resectable disease (1). Over the past two decades, the regimes of cisplatin and etoposide and carboplatin and paclitaxel with or without cetuximab have been most widely used, with cisplatin and vinorelbine with radiotherapy as possible alternative. More recently interest in the cisplatin/pemetrexed/radiotherapy combination has gained interest based on the superior toxicity and efficacy profile of this approach compared to platinum-based non-squamous cell malignancies (2). In addition, it is possible to administer this combination of drugs at systemic doses together with radiotherapy (3). In the randomized phase III PRONOUNCE study, this regimen was directly compared with etoposide and cisplatin. The goal of this trial was to establish the feasibility of this regimen. The trial was closed prior to full enrollment, with approximately 300 patients per arm evaluated, due to futility for superiority. Median survival for both study groups was very similar at 26.8 and 25.0 months, respectively and better than statistically assumed (4). Additional chemoradiotherapy regimes of current interest include the addition of the cell cycle inhibitor velparib to cisplatin and paclitaxel in the phase III (5). Over the last decade, systemic therapy for patients with metastatic lung cancer has been transformed through the use of tumor mutation analyses and targeted therapies as well as the emergence of immune-oncology. However, application of these strategies to the stage III setting has been slow and no definitive data exist currently to support these strategies in the curative intent setting. The addition of cetuximab to chemoradiotherapy did not result in improved survival. Additional chemotherapy or targeted therapy in this setting, as well as in the chemoradiotherapy setting in the stage IIIA and IIIB setting is needed.
in a survival benefit in RTOG 0612 (6). There are, however, several ongoing trials that will be described, including RTOG 1306–Alliance 31101. In this trial patients with EGFR mutation or an alk translocation are randomized to either concurrent chemoradiotherapy with the appropriate targeted agent (erlotinib and crizotinib, respectively) followed by concurrent chemoradiotherapy or concurrent chemoradiotherapy alone. This trial is actively accruing patients. Regarding immune-oncology, a trial evaluating a lipidosome-based MUC vaccine (tecemotide) has been completed. MUC1 is a mucinous glycoprotein that is overexpressed in NSCLC and a vaccine strategy was supported by preclinical studies as well as clinical data in a stage III subgroup analysis of an earlier exploratory trial. Butts et al (7) reported on a randomized trial in which patients completing locoregional sequential or concurrent therapy were randomized to placebo versus cetuximab concurrent with radiation, reporting a trend for improved overall survival that was statistically significant in the subset analysis of patients receiving concurrent radiotherapy as their primary therapy. Further investigations of this agent however were halted following emerging of additional negative data from a Japanese phase II trial that remains unpublished. Regarding PD-1 or PD-L1 inhibitors, trials have recently been activated investigating the addition of such agents in the consolidation setting following primary treatment of patients with unresectable SCLC. For example, in the ‘Pacific’ trial patients are randomized in a 2:1 fashion to durvalumab for up to 12 months or placebo. In the Alliance, a trial looking at induction chemotherapy with atezolizumab plus thoracic radiation is currently in the process of accrual. Here patients will receive induction chemotherapy with atezolizumab for up to four cycles followed by concurrent chemoradiotherapy and additional adjuvant immune therapy. These strategies are well supported by preclinical data showing irradiation upregulates the expression of and tumor cells and synergy with amplification of radiation antitumor effects by PD-L1 blockade (8). Updated information on these trials and relevant preclinical data will be presented.


Keywords: radiation sensitivity, Stage III NSCLC, concurrent chemoradiotherapy

SESSION ED11: ADVANCED NSCLC: STATE-OF-THE-ART TREATMENT WEDNESDAY, DECEMBER 7, 2016 - 11:00-12:30

ED11.01 SYSTEMIC THERAPY FOR ADVANCED ONCOGENE-DRIVEN NSCLC

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3Department of Medical Oncology, BC Cancer Agency Vancouver Centre, Vancouver/Canada

Oncogene-driven lung cancer remains the embodiment of personalized medicine. Since the first description of EGFR activating mutations found in patients with what was then called bronchioloalveolar carcinoma of the lung (BAC) in 2004, the topic of oncogene-driven lung cancer has grown rapidly and expanded to now encompass a number of additional mutation- and fusion-related entities. Recent updates to molecular testing guidelines, such as those of IASLC, have added several new oncogenes to the initial EGFR and ALK recommendations, including RDS1 and RET fusions, MET amplification or mutation, and HER2 mutations (1,2,3). Although the efficacy of tyrosine kinase inhibitors (TKI) in the treatment of some of these disease subsets is well established, the treatment decision-making process at the time of relapse is becoming more complex as our knowledge of resistance pathways grows and more treatment options become available, with 2nd and 3rd generation drugs now in play. Subtyping of progressive disease (PD) in oncogene-driven lung cancer into systemic PD versus oligo-PD or CNS-satuary PD can assist in determining the most appropriate therapeutic approach, as shown in Figure 1 below(4). Further, the methods by which we assess tumor at the time of initial or re-biopsy are also rapidly evolving, from single gene or multiplexed gene panels to highly sensitive and specific next generation sequencing (NGS). Lastly, we and others (4,5) have proposed algorithms for possible substitution of plasma cell free DNA by NGS platforms for tissue re-biopsy or for serial monitoring in a survival benefit in RTOG 0612 (6). There are, however several ongoing clinical trials that will be described, including RTOG-1306 and ALK-rearranged subsets, since the treatment paradigms are most well established. We will emphasize some of the real world challenges faced by treating physicians. Decision criteria for selecting the best first-line therapy will be reviewed, the importance of re-biopsy upon disease progression to determine the most appropriate next line therapy highlighted, and third line therapy and beyond discussed. The emerging role of liquid biopsy for assessment of plasma cell free DNA will be discussed, as well as a rationale for substituting liquid biopsy for initial or repeat tumor biopsy in some clinical settings. Algorithms designed to facilitate treatment decision-making will be presented. Two examples in EGFR-mutated lung cancer are shown below.

Figure 1: Algorithm for management by Progressive Disease Subtyping EGFR-mutated NSCLC

In EGFR-mutated NSCLC

Keywords: radiation sensitivity, Stage III NSCLC, concurrent chemoradiotherapy

Figure 2: Algorithm for Re-Biopsy and/or Plasma cfDNA Analysis

In EGFR-mutated NSCLC
SESSION ED12: REGIONAL TOBACCO CONTROL POLICIES: ADVANCES & CHALLENGES
WEDNESDAY, DECEMBER 7, 2016 - 11:00-12:30

ED12.01 TOBACCO CONTROL POLICIES IN EASTERN EUROPE
Gábor Kovács, Zsuzsa Cselkö
National Korányi Institute for TB and Pulmonology, Budapest/Hungary

According to the regional distribution of the World Health Organization (WHO), Europe extends from the Atlantic Ocean to Central Asia, encompassing states of the former Soviet Union. In political terms however, Eastern Europe refers to countries located on the eastern border of the European Union (EU). Consequently, in our presentation we focus on how smoking status has changed in some of the policy-wise emerging countries located here – namely the Czech Republic, Hungary, Poland and Romania – and how these data compare to Austria’s indicators. We present data on smoking prevalence and trends, restricting use, taxation and average cigarette prices, as well as the distribution of tobacco products in specific countries. Reference is made to restricting advertising and tobacco industry sponsorship activities. Smoking cessation support practice is another important aspect, while electronic cigarette (e-cigarette) regulation is a relatively new issue. Table 1 presents smoking prevalence and trends of specific countries.

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<th>Year</th>
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<td>1980</td>
<td>26.2</td>
<td>34.8</td>
<td>42.5</td>
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<td>1996</td>
<td>26.6</td>
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<td>33.7</td>
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<tr>
<td>2006</td>
<td>26.3</td>
<td>32.9</td>
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<td>2012</td>
<td>24.4</td>
<td>28.5</td>
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<td>32.3</td>
</tr>
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</table>

Table 1. Smoking prevalence (%) (≥15 years old) is it striking that while the proportion of smokers has decreased in Hungaty and Poland, an opposite tendency may be observed in Austria. Smoking prevalence stagnated in Romania and the Czech Republic. It is noteworthy that the proportion of women smokers is high in Austria (28.3%), in Hungary (25.8%) and in Poland (24.2%). Smoke-free laws were adopted in the beginning of this Century in North American and European countries. Following the establishment of Turkish Republic in 1923, the State Monopoly on tobacco was established and tobacco production and sales was nationalized by the government, therefore production and sales of tobacco was planned and implemented by the State Monopoly (TEKEL). Only domestic tobacco products were on sale in the country, and importation and sales of foreign tobacco products was not allowed. TEKEL provided tobacco products for the smokers, but did not make any effort to increase the use. It was not allowed to make any advertisement of tobacco. The tobacco monopoly has been the only responsible body on tobacco production and sales, until 1980’s. In 1984 the law passed at the Parliament allowing importation of foreign cigarettes into the country, and then tobacco advertisements started. In 1987 Minister

References

Acknowledgements
This study was carried out within Transregio 130, funded by the German Research Foundation (DFG).

Keywords: smoking control policies, smoking prevalence

ED12.02 TOBACCO CONTROL: THE TURKISH EXPERIENCE
Nazmi Bilir
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Turkey has been a tobacco producing country since Ottoman time. At that time tobacco production mostly was in the hands of foreign companies. Following the establishment of Turkish Republic in 1923, the State Monopoly on tobacco was established and tobacco production and sales was nationalized by the government, therefore production and sales of tobacco was planned and implemented by the State Monopoly (TEKEL). Only domestic tobacco products were on sale in the country, and importation and sales of foreign tobacco products was not allowed. TEKEL provided tobacco products for the smokers, but did not make any effort to increase the use. It was not allowed to make any advertisement of tobacco. The tobacco monopoly has been the only responsible body on tobacco production and sales, until 1980’s. In 1984 the law passed at the Parliament allowing importation of foreign cigarettes into the country, and then tobacco advertisements started. In 1987
of Health invited some interested scientists to discuss the way to control tobacco use in the country. The first tobacco control law was drafted by the Ministry and adopted at the Parliament in 1991; but vetoed by the President. Same year another law passed from the Parliament to allow multinational tobacco companies to establish tobacco production factories in the country. As the result of these changes, tobacco use started to increase, more than the population increase (Table 1) (1). The first large-scale survey in 1988 (2) on tobacco use revealed that 63% of males and 24% of females smoke. Table 1. Cigarette sales, Turkey, 1925 - 2011 As reaction to these huge numbers, a civil society organization was established in 1993, “National Coalition on Tobacco or Health, SSUK”. By this way an organized fight against the multinational tobacco companies started. In 1995 a large scale survey on tobacco use among role model groups revealed that 43% of physicians, almost 50% of teachers, 27% of members of the Parliament and 26% of religious leaders were smoking (3). At the same time, draft tobacco control law was in the agenda of the Parliament. SSUK worked closely with some of the “sensitive” MPs’, participated in the Parliamentary Commissions to discuss the draft tobacco control law, and visited Head of the Parliament, Parliamentary Groups of the political parties. At the end of these efforts, Tobacco Control Law was adopted by the Parliament in November 1996. The Law banned smoking in some of the indoor public places, i.e. health and education facilities and public transport, banned all kinds of advertisement and promotion of tobacco products, banned selling of tobacco products to children, etc. After more than 10 years of introduction of first law and amendment law (2002) and 2012 (5 years after smoke-free policy, and 20 years period between 1993 and 2012) smoking prevalence was reduced during the 20 years period between 1993 and 2014, pace of decrease slowed recently. More than 10 years of introduction of first law and amendment law (2002) and 2012 (5 years after smoke-free policy, and 20 years period between 1993 and 2012) smoking prevalence was reduced during the 20 years period between 1993 and 2014, pace of decrease slowed recently. More than 10 years of introduction of first law and amendment law (2002) and 2012 (5 years after smoke-free policy, and 20 years period between 1993 and 2012) smoking prevalence was reduced during the 20 years period between 1993 and 2014, pace of decrease slowed recently. More than 10 years of introduction of first law and amendment law (2002) and 2012 (5 years after smoke-free policy, and 20 years period between 1993 and 2012) smoking prevalence was reduced during the 20 years period between 1993 and 2014, pace of decrease slowed recently. More than 10 years of introduction of first law and amendment law (2002) and 2012 (5 years after smoke-free policy, and 20 years period between 1993 and 2012) smoking prevalence was reduced during the 20 years period between 1993 and 2014, pace of decrease slowed recently. More than 10 years of introduction of first law and amendment law (2002) and 2012 (5 years after smoke-free policy, and 20 years period between 1993 and 2012) smoking prevalence was reduced during the 20 years period between 1993 and 2014, pace of decrease slowed recently. More than 10 years of introduction of first law and amendment law (2002) and 2012 (5 years after smoke-free policy, and 20 years period between 1993 and 2012) smoking prevalence was reduced during the 20 years period between 1993 and 2014, pace of decrease slowed recently. More than 10 years of introduction of first law and amendment law (2002) and 2012 (5 years after smoke-free policy, and 20 years period between 1993 and 2012) smoking prevalence was reduced during the 20 years period between 1993 and 2014, pace of decrease slowed recently.
Abstracts

ED12: REGIONAL TOBACCO CONTROL POLICIES: ADVANCES & CHALLENGES
WEDNESDAY, DECEMBER 7, 2016 - 11:00-12:30

ED12.06 TOBACCO CONTROL POLICIES IN LATIN AMERICA
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Introduction: Smoking is the single most important cancer risk factor and accounts for 26% of all cancer deaths and 84% of lung cancer deaths in Latin America. Lung cancer is one of the most preventable cancer types; and doctors of all expertise are essential to impart to patients and their families the idea of smoking prevention, thereby contributing to the reduction of mortality from lung cancer. There are around 145 million smokers age 15 years or older in Latin American. Adult smoking prevalence varies from 35% in Chile and 30% in Bolivia to 11% in Panama and 11% in El Salvador6. The continuing popularity of smoking among adolescents is particularly worrisome as smoking rates among young people aged 13–15 years are now higher among youth in all Latin American countries. Prevalence among adolescent females has surpassed their male counterparts in Argentina, Brazil, Chile, Mexico, and Uruguay. Unless these high rates of smoking are curtailed, cancer mortality rates will continue to rise7. We have assessed the impact on smoking rates of anti-tobacco policies adopted by five Latin American countries, in compliance with the WHO's Framework Convention on Tobacco Control (FCTC). Argentina, Brazil, Mexico, Peru, and Uruguay were used as case studies to illustrate the influence of the FCTC on the tobacco industry and on the government. The degree of implementation and the level of enforcement of anti-smoking policies, tobacco farming, compliance with the terms of the Convention seems to have a direct impact on the reduction of smoking rates in the countries studied. Other solutions should contemplate tobacco farmers, whose fear of shifting to new unfamiliar tobacco products is high taxation (over 75%) of tobacco products12. Conclusion: The degree of compliance with the terms of the Convention seems to have a direct impact on the reduction of smoking rates. Other solutions should contemplate tobacco farmers, whose fear of shifting to new unfamiliar cultures is exploited by the tobacco industry to prevent FCTC ratification in many countries. But farmers should not stop growing tobacco plants, but just shift to transgenic tobacco farming13,14.

ED13.02 TISSUE-BASED BIOMARKERS
Glen Reid1, Steven Kao1, Nico Van Zandwijk1
1Asbestos Diseases Research Institute, Sydney/Australia; 2Medical Oncology, Chris O'Brien Lifehouse, Sydney/Australia

Introduction: Malignant pleural mesothelioma (MPM) is difficult to diagnose and accurate prediction of patient outcomes still relies on a range of clinical scores. Despite extensive efforts in the last decade, there are few tumour-based molecular markers that can accurately contribute to diagnosis and prediction of disease course. Recent reports describing the mutational and transcriptional landscape of MPM tumours have revealed a number of changes that may yield clinically useful biomarkers following further development and validation studies. Diagnosis: The definitive MPM diagnosis relies on a tissue biopsy and demonstration of invasion. Diagnostic markers consist of a combination the expression of mesothelial-specific proteins and absence of markers of adenocarcinoma. Recent advances have shown that the mutation of the tumour suppressor BAP1 leads to loss of nuclear staining, and that this is highly specific for discriminating mesothelioma from benign conditions. As in some cases MPM has neither BAP1 loss nor loss of nuclear staining, sensitivity is lacking, but this can be improved by incorporating detection of CDKN2A genomic loss using FISH. Assessment of additional mutations and fusion genes recently identified in MPM may represent useful markers for future development. Characteristic changes in microRNA expression are present in MPM, and these form the basis of a highly accurate molecular test for the differential diagnosis of MPM from other tumours affecting the pleura. Prognosis: Clinical and pathological

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parameters remain the best predictors of disease outcome, and although some molecular markers have demonstrated prognostic significance, these are yet to be validated. Histopathological subtype is an accurate prognostic indicator, with the epithelioid subtype associated with significantly better outcomes than the non-epithelioid biphasic and sarcomatoid types. The variation within epithelioid tumours is well recognised, and epithelioid tumours with a pleomorphic morphology have poor prognosis, similar to patients with non-epithelioid tumours. Recent results from transcriptomic analyses have identified sub-sets within epithelioid tumours which more accurately describe prognosis. These include the two-cluster C1/C2 classification system based on a 3 gene predictor, and the 4 clusters (sarcomatoid, epithelioid, biphasic-epithelioid and biphasic-sarcomatoid) derived from RNA-seq analysis. MicroRNA expression has also been linked to outcome. Early studies have suggested that significant changes in miR-29c-3p, with higher levels corresponding to longer survival. More recently, microRNA expression profiles differing between long and short survivors yielded a 6-microRNA score that predicted outcome in two surgical series. Whether TCGA data confirm these observations remains to be determined. In addition to RNA and protein biomarkers, the cellular composition of tumours influences patient outcomes. It is likely that the mix of cell types within tumour samples also contributes to biomarker expression, especially for RNA extracted from whole tumours. For some proteins, differential expression in the stromal and tumour compartments is of prognostic value, for example in the case of SPARC expression. Inhibiting candidates targeting cell infiltrate was recently investigated in a large number of epithelioid samples revealing that greater numbers of tumour-infiltrating CD4+ and CD8+ T lymphocytes (TILs), as well as fewer tumour-associated macrophages (TAMs), are associated with survival. In addition, the reuced folate carrier (RFC) was also shown to predict outcome in epithelioid MPM. Other cell populations associated with vascular and lymphatic invasion are also linked to survival. Prediction: Unlike lung cancer, few actionable mutations are present in MPM that predict sensitivity to targeted agents, and clinical trials with these agents have failed to yield disappointing results. Single agent chemotherapy and the standard cisplatin/pemetrexed doublet have also been investigated in retrospective studies attempting to link patient outcomes with gene (mRNA and protein) expression and polymorphisms. Multiple reports have linked levels of TS protein, but not mRNA, to outcomes with some studies suggesting that it may be overexpressed from a mutated cell line. Other levels of other proteins such as folypolyglutamate synthase (FGPS) and the reuced folate carrier (RFC) were also associated with tumour response and patient outcomes. However, a subsequent study with a similar number of patients suggested that both TS and FGPS lack predictive value. With respect to DNA repair genes involved in cisplatin activity, ERCC1 and others have been evaluated, but results are again inconclusive. The picture is complicated by assessment of target genes in patients treated with two interacting agents (with or without subsequent surgery), and the true value of these genes awaits carefully controlled prospective analyses. The recent breakthrough in cases of SPARC checkpoint inhibiting antibodies targeting CTLA4 and the PD-1/PD-L1 axis in melanoma and lung cancer has seen these agents applied to MPM patients. With response rates of around 25% for PD-1 targeting antibodies pembrolizumab and nivolumab in MPM, new predictive markers are being sought to improve the effect of single agent chemotherapy and the standard cisplatin/pemetrexed doublet. Other potential targets include the presence of T-regulatory cells (Tregs) and the ratio of the M1 to M2 type correlates with survival. In addition, the ratio of the CD4+ to CD8+ T lymphocytes is of prognostic value, for RNA extracted from whole tumours. For some proteins, differential expression in the stromal and tumour compartments is of prognostic value, for example in the case of SPARC expression. The importance of the immune expression in the stromal and tumour compartments is of prognostic value, for example in the case of SPARC expression. The importance of the immune

Keywords: predictive markers, diagnosis, Prognosis

ED13.04 SYSTEMIC INDUCTION THERAPY OF MALIGNANT PLEURAL MESOTHELIOMA

Paul Baas
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Over the last 3 decades clinical researchers have focused on the optimal treatment of patients with mesothelioma (MPM). In the 80’s surgery had become a standard approach in some centers but it became clear that a complete resection (R0) was not achievable. The anatomical location of the mesothelioma simply does not allow a resection with save margins of normal tissue. Therefore additional therapies were looked for and a different number of approaches were evaluated. To analyze the different approaches any systemic induction therapy is considered the best, this can be answered with a clear No. Reasons for this is the lack of randomized studies in this patient population and the fact that patients with MPM are grouped together despite differences in pathology, surgical approach (EPP vs Pleurectomy derortomy) and non-random treatment. In the last decade a number of preferential approaches with chemotherapy in this disease ranging from Induction chemotherapy; Intracavitary therapy and Adjuvant chemotherapy. (table) In the case of induction therapy it is clear that one aims at reducing the tumor bulk and to prevent metastases during surgery. The preferred treatment is cisplatin with pemetrexed since this is considered to be the standard of this disease. (1) Other regimens have been tested in small extend but usually involved. The use of intra-cavitary treatment has attracted attention since MPM cells show the tendency to stay localized in the thoracic cavity for a relative long period. The administration of a local cytotoxic drug would allow an improvement in local control and limited systemic effects. Cisplatin has been used frequently during surgery and were combined with heating of the lavage fluid to 40°Celsius. (2) Special precautions for this so-called Hyperthermic laveage approach have to be taken in the operating suite with protection of the staff to avoid exposure to the drugs. In general the laveage procedure adds another hour to the debulking surgery. Measurements of platin adducts in the blood during this procedure have shown that there is no important systemic levels measured. Unfortunately there has not been any comparison of these approaches. Most series only report the feasibility of the treatment with some times impressive survival figures. These are partly due to the strong selection of patients for the studies. A relative new approach is the use of a platin containing fibrin glue that can be applied to the thoracic wall after debulking using a spray system. The initial results indicate that the treatment is fast and serial biopsies show that the effect is sustained for many weeks. (3) Finally it is clear that cisplatin and cisplatin based chemotherapy can be applied. In this field there are no data to support any specific treatment and the choices are generally defined based on the study protocol. No prospective trials have been reported

Most of the studies are trimodality therapies where RT is an important part of the protocol. One typical example is the EORTC study where the feasibility of trimodality therapy in a phase II trial (EORTC 080301) with clearly defined timelines was tested(5). Patients with pathologically proven mesothelioma received induction chemotherapy (3 courses cisplatin and pemetrexed) followed by EPP within 21-36 days after the last dose of chemotherapy in the absence of progressive disease and unacceptable toxicity. “A success of treatment” was defined as a patient who had received the full protocol and was alive after 90 days without progressive disease and without grade 3 or 4 toxicity. Of the 57 patients included, 42 had EPP (73.7%) after induction therapy. The 90-day mortality was 6.5% with an overall survival time of 18.4 months and progression-free median survival time of 13.9 months. Only 24 (42.1%) patients met the definition of success, thereby failing the primary endpoint. This study showed how difficult it is to complete a trimodality study in this patient group and only when a standard is defined, proper comparative studies can be performed. Other important studies addressing the neo-adjuvant approach are presented in the table.

3. Opitz I. Use of fibrin glue in malignant pleural mesothelioma, presented at the xth IMIG conference Birmingham UK

(See Table next page)
### Study | Type | a pts | Drugs | Completed Chemotherapy | Completed Surgery | Completed Radiotherapy | Outcome (MOZ)
--- | --- | --- | --- | --- | --- | --- | ---
SAKK 17/04 Lancet Onc 2015;16:1651 | Neo-adj | 151 | Cis/pem | 145 | 125 | 23/27 in 2nd stage | 7.6-9.4
Frederico BMC Cancer 2013;13:22 | Neo-adj | 54 | Cis/pem | 96% | 83% | 41% | 15.5
Krug JCO 2009;27:3007 | Neo-adj | 77 | Cis/pem | 83% | 74% | 52% | 16.8
Weder JCO 2004;22;3451 | Neo-adj | 20 | Cis/gem | 90% | 80% | n.a. | 23
Van Schil ERJ 2010;36:1362 | Neo-adjvant | 59 | Cis/pem | 93% | 79% | 65% | 18.4
Richards JCO 2006;24;1561 | Intracavitary | 61 | Cisp 50-225 | n.a. | 72% | 9.0
Tillemann JTCS 2009;138:405 | Intracavitary | 121 | Cisp 225 | n.a. | 79% | n.a. | 12.8

**Keywords:** surgery; mesothelioma; chemotherapy

### ED13.05 SYSTEMIC THERAPY OF INOPERABLE MALIGNANT PLEURAL MESOTHELIOMA

**Arnaud Scherpereel**

Pulmonary and Thoracic Oncology, Hospital of the University (CHRU) of Lille, Lille/ France

To date, the treatment of malignant pleural mesothelioma (MPM), a rare and aggressive tumor usually induced by previous asbestos exposure, relies mostly on chemotherapy and/or immunotherapy. But exciting drugs and strategies were tested in this testing, in particular ICI. A phase III trial (Polaris), comparing first line Cis/Pem with ADI-PGEO 20 or placebo, will start in 2017 for biphasic (mixed) or sarcomatoid MPM only because they exhibit ASS-1 defect twice more frequently than epithelioid subtype. Finally, other innovative drugs also candidates for first line treatment in combination with Cis/Pem, after preliminary positive clinical trials, include gene therapy, cell therapy using chimeric antigen receptors (CARs) or dendritic cells (DC), or oncotherapy, and will be assessed as first line treatment in MPM very soon or later. For example, the European “DENIM” phase III trial will test DC based immunotherapy with allogenic tumor cell lysate as maintenance treatment after Cis/Pem chemotherapy in MPM patients. But, as in lung cancers, immune checkpoint inhibitors (ICI) seem to represent presently the most exciting tool for MPM patients. In fact, even if a recent, large phase II trial (n=566, “Determine”) with anti-CTLA-4 mAb (tremelimumab) versus placebo in 2nd/3rd line treatment did not meet its first endpoint (mOS) (21), early data of a phase Ib basket trial with anti-PD-1 mAb (pembrolizumab) showed promising response rate (RR) of 28% and DCR of 76% in PD-L1 positive MPM (22). Other trials with checkpoint inhibitors are ongoing with anti-PD-1 alone (nivolumab, pembrolizumab), or a combination of anti-PD-1 (nivolumab) or anti-PD-L1 (durvalumab) and anti-CTLA-4 (tremelimumab or ipilimumab) as first or 2nd/3rd line treatment. Interestingly, new clinical trials are already underway to assess value of ICI, such as nivolumab + ipilimumab combo, versus Cis/Pem as first line treatment. In conclusion, the triplet cisplatin/ pemetrexed/bevacizumab may be a new first line standard of care for patients eligible for bevacizumab, and not candidate to multimodal treatment. Second line and further lines treatments are very limited with no validated options except pemetrexed in case of late relapse after platinum/ pemetrexed. But exciting drugs and strategies were tested in this testing, in particular ICI. But remaining key questions include which predictive biomarkers for these innovative, thrilling but expensive treatments to target the best patients for each drug? And how to potentially combine these drugs versus, or in combination with, standard chemotherapy? Thus real hopes seem closer for our MPM patients with new systemic treatments.

**Keywords:** Mesothelioma, chemotherapy, Immunotherapy, systemic treatment

### ED13:TREATMENT OF MALIGNANT PLEURAL MESOTHELIOMA

**ED13.06 MESOTHELIOMA IN A SETTING OF GERMLINE BAP1 MUTATIONS**

**Michele Carbone1, Harvey Pass2, Haining Yang1**

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Individuals that are born with germline BAP1 mutations are affected by the BAP1 cancer syndrome. All individuals affected by this cancer syndrome have developed one or more malignancies in the course of their life. Mesothelioma, uveal and cutaneous melanomas - tumors often associated with exposure to environmental carcinogens, are the most common malignancies, although almost any tumor type has been detected in carriers of this cancer syndrome. In addition, BAP1 mutant carriers develop multiple benign melanocytic tumors - histologically different from other SPITZ-like tumors; that we have called melanocytic BAP1 associated intradermal tumors (MBAITs) that can...
alert the physician that the patients is a carrier of the BAP1 cancer syndrome. Most malignancies develop after the 4th decade of life, although cancers in individuals as young as 19 years old have been detected. Because many of these malignancies, for example melanomas, can be cured by early detection, it is important to identify BAP1 mutant carriers that can be screened for early detection and curative resection. Moreover, carriers of germline BAP1 mutation may be at increased risk of developing mesothelioma and melanoma following exposure to low doses of asbestos, sunlight and X-Rays, thus cancer prevention measures can be implemented. When cancer develops in a setting of BAP1 germline mutations, these patients have a much better prognosis compared to patients with the same malignancies when they occur sporadically (i.e., not in carriers of BAP1 mutations). Familial mesotheliomas in these individuals occur in either the pleura or peritoneum (frequency ratio 1:1) at a median age of 56.3 years, have a male-to-female ratio of 0.73:1, and are associated with prolonged survival of 5 to 10 or more years, compared with a median age at diagnosis of 72, a pleural-to-peritoneal ratio of 86:1, a male-to-female ratio of 4:1, and a median survival of less than 1 year in sporadic mesothelioma. About 100 families with this mutated BAP1 cancer syndrome have been described in the United States, Europe, and New Zealand. Genetic studies demonstrated that these mutations are transmitted across multiple generations over the course of several centuries, and some US families carrying BAP1 mutations descend from a Swiss family that immigrated in the US in the early 1700s. An International Consensus Meeting sponsored by the IASLC supported medical screening for at-risk people who are carriers of BAP1 germline mutations as follows: (1) annual dermatological screening for early detection of melanoma at age 18 or younger; (2) annual eye examination/ophthalmoscopy for uveal melanoma at age 18 or younger; and (3) skin and eye examinations every 6 months after age of 30, when the frequency of cancer among carriers of germline BAP1 mutations starts to increase. It was also recommended that genetic counseling should be offered to all individuals tested for BAP1. Moreover, those with BAP1 germline mutations should be encouraged to participate in studies to improve early detection of mesothelioma (Larsson M. et al., Journal of Thoracic Oncology 11, 1246-1262, 2016).

Keywords: BAP1, mesothelioma, germline

SESSION ED14: SMALL CELL LUNG CANCER
WEDNESDAY, DECEMBER 7, 2016 - 14:30-15:45

ED4.01 CHEMOTHERAPY OF SMALL CELL LUNG CANCER
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Small cell lung cancer, which accounts for 10-15% of all lung cancers, is a biologically and clinically virulent malignancy that has the potential to disseminate systemically and therefore is often initially diagnosed at an advanced incurable stage. Although typically associated with heavy tobacco use, there have been recent clinical observations of histologic evolution from adenocarcinoma to a SCLC phenotype, particularly in tumors harboring activating mutations in the epidermal growth factor receptor (EGFR) gene that had been treated with EGFR inhibitors. Due to its high proliferative rate, SCLC is known to be highly responsive – at least initially - to cytotoxic chemotherapy. Tumor response rates of 50-70% following platinum-based chemotherapy are usually expected. Intracranial metastases, a common feature of ES-SCLC, have been also shown to respond at a similar rate to cytotoxic therapy as that of metastases to other visceral organs. The standard frontline chemotherapy for ES-SCLC, unchanged for the past three decades, has been platinum-based (either cisplatinum or carboplatin) plus etoposide. No other regimen has convincingly been demonstrated to be superior to platinum-etoposide in the frontline setting. Neither dose intensification approaches nor the incorporation of other cytotoxic agents into the platinum backbone have yielded any palatable or tangible survival benefits. In recent years, only prophylactic cranial irradiation (and in highly selected patients) has been associated with a marginal improvement in survival outcomes. Furthermore, despite the high initial response rates to chemotherapy, drug resistance and subsequent tumor progression are universal events. Following failure of frontline platinum-based therapy, the options are limited and generally considered inferior. Current investigations into optimizing cytotoxic therapy include the development of novel cytotoxic agents that involve novel "targeted" therapies and immunotherapeutics such as checkpoint inhibitors, or conjugating a cytotoxic payload onto monoclonal antibodies directed against an antigen expressed on SCLC, among others. A critical appraisal of the current status and future directions of cytotoxic therapy in ES-SCLC will be presented.

Keywords: SCLC, small cell, neuroendocrine

ED14.02 THORACIC RADIOTHERAPY OF SCLC
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Limited stage: Small cell lung cancer (SCLC) comprises 10-15% of all lung tumors and is associated with an aggressive clinical behavior. Two out of three patients present with hematogenous metastases at diagnosis (extensive stage (ES)). For patients without hematogenous metastases (limited stage (LS)), chemoradiotherapy is the standard treatment. Although radiotherapy after chemotherapy has the theoretical benefit of treating smaller target volumes with less toxicity, concurrent chemoradiotherapy has shown to be superior. Moreover, earlier use of systemic therapy during chemotherapy phase may lead to better results. The absolute benefit of early versus late radiotherapy was about 10% for patients who had received cisplatinum-based chemotherapy [1]. Turrisi et al. [2] demonstrated that twice daily radiotherapy starting with a first course of chemotherapy resulted in improved survival rates. Median survival was 23 months for patients who received twice-daily radiotherapy (45Gy/30fractions/3weeks) versus 19 months for once daily treated patients (45Gy/25fractions/Sweeks). The corresponding 5 years survival rates were 26% and 16%. However, more Grade 3-4 oesophagitis was seen during twice-daily treatment (32% versus 16%). Only a minority of patients in the US and Europe receive twice daily radiotherapy. Recently the results of the CONVERT trial, in which once-daily radiotherapy (70Gy) was compared with twice daily radiotherapy (45Gy) were presented [3]. Radiotherapy was initiated at the 2nd course of 4-6 cycles of cisplatin/etoposide. There was no statistically significant difference in overall survival between the two arms. Overall survival at 2 years was 50% for patients treated once daily versus 51% for patients treated once daily (p=0.15) [3]. There was also no significant difference in time to progression. There were no differences in a acute toxicity, except for Grade 3-4 neutropenia, which occurred more often in the twice-daily treatment arm (74% versus 65%). There were no differences in grade 5 oesophagitis (15%) and grade 5 pulmonary toxicity (15%). The authors concluded that survival in both study arms was higher than reported previously and that radiation related toxicities were lower than expected, probably related to the use of modern radiotherapy techniques. The results of the study support the use of either twice daily or once daily as standard of care for patients with limited stage disease and in good performance score. In RTOG0538 study, which also compares 70 Gy once daily and 45 Gy twice daily radiotherapy, radiotherapy commences with the first or second course of chemotherapy. The results of this study are eagerly awaited [4]. Extensive stage: In the EORTC study on prophylactic cranial irradiation (PCI) for a limited stage of disease, the vast majority of patients still had intrathoracic disease after completion of chemotherapy. After on the positive effects of PCI which not only reduced the risk of symptomatic brain metastases (40 versus 15%) but also improved overall survival (1 year: 27 versus 13% (P=0.003) [5], the next logical step was to investigate the use of thoracic radiotherapy in combination with PCI. It was demonstrated for a possible role of thoracic radiotherapy (RT) in ES-SCLC also from the results of a trial published by Jeremic et al. in 1999 [6] in which patients with ES-SCLC and good prognosis with a complete response outside the thorax were randomized between TRT plus PCI during chemotherapy versus chemotherapy and PCI only. The overall survival was 14 months for those who received thoracic radiotherapy versus 11 months for those who did not. In the CREST trial, patients with ES-SCLC and any response after 4-6 cycles of platinum based chemotherapy were randomized between PCI plus TRT (30Gy/10 fractions) or PCI only. Overall survival at one year, the primary endpoint of the study, was not statistically significant between the groups (p=0.066) but with longer follow up the survival curves diverged and at 2 years, survival was 13% in patients who received TRT versus 3% in the controls (p=0.004). There was also significant difference in progression free survival. In an additional analysis of patients with and without residual intrathoracic disease, which was one of the stratification factors of the study, it was demonstrated that there was no significant benefit of TRT in patients with a CR in the thorax. However, in patients with residual intrathoracic disease after chemotherapy, TRT led to a significant improvement in overall survival [7]. Patients who received thoracic radiotherapy the risk of intrathoracic recurrence was reduced from 80% to 44%. In patients who received thoracic radiotherapy the most recurrences occurred outside the brain and the thorax and at a later stage. The next logical step after demonstration of a beneficial effect of PCI and TRT would be the use of higher doses for TRT and possibly also treatment of extrathoracic metastatic sites. This topic was also recommended that genetic counseling should be offered to all individuals tested for BAP1. Moreover, those with BAP1 germline mutations should be encouraged to participate in studies to improve early detection of mesothelioma (Larsson M. et al., Journal of Thoracic Oncology 11, 1246-1262, 2016)
for patients from the top accruing centers from the CREST trial. An evaluation of 260 patients showed significantly better outcome in patients with 0 to 2 metastases versus and without liver metastases [10]. These patients are believed to be best candidates for future studies. References:


Keywords: SCLC, thoracic radiotherapy, Radiotherapy

ED14: SMALL CELL LUNG CANCER
WEDNESDAY, DECEMBER 7, 2016 - 14:30-15:45

ED14.03 UPDATE ON PROPHYLACTIC CRANIAL IRRADIATION IN SCLC
Takashi Seto
Department of Thoracic Oncology, National Kyushu Cancer Center, Fukuoka/Japan

Background: A previous study has shown that prophylactic cranial irradiation (PCI) reduced the risk of brain metastases (BM) and prolonged the overall survival (OS) of patients (pts) with extended disease small cell lung cancer (ED-SCLC). However Japanese trial to reconfirm these results was stopped at first interim analysis (n=163) pts because of futility. According to this study protocol, final follow up was done.

Materials and methods: From March 2009 pts with ED-SCLC who had any response to first-line chemotherapy (platinum agent plus irinotecan or etoposide) were randomized to either PCI (25Gy/10 fractions) or observation (Obs) alone. The patients were required to prove the absence of BM by MRI prior to enrollment. The primary endpoint was OS and planned sample size of 330 was determined to detect the hazard ratio (HR) of 0.75 at a significance level of 0.05 and a power of 80%. Secondary endpoints included time to BM (evaluated every 3 months by imaging), progression-free survival (PFS), and adverse effects (AEs) and mini mental status examination (MMSE).

Results: In Apr 2014, follow up analysis was conducted for the survival data of 224 all enrolled pts. One hundred four-five deaths were observed. The median OS was 11.6 and 14.1 months for PCI (n=112) and Obs (n=111), respectively (HR=1.25, 95%CI=0.95-1.62; stratified log-rank test, P=0.107). PCI significantly reduced the risk of BM compared to Obs (33.6% vs 52.7% at 12 months; Gray’s test, P<0.001), whereas PFS was comparable between the two arms (median, 2.3 vs 2.4 months; HR=0.98, 95%CI=0.75-1.28). No significant difference in AEs greater than Grade 2 was observed between the two arms. As the MSME there was no statistical difference between two arms, however in pts age 70 and older in PCI tended to be worse over time.

Conclusion: PCI after response to chemotherapy could not show the OS impact in pts with ED-SCLC even in this follow up data.

Keywords: phase III, overall survival, SCLC, PCI

ED14: SMALL CELL LUNG CANCER
WEDNESDAY, DECEMBER 7, 2016 - 14:30-15:45

ED14.04 IS THERE A ROLE FOR SURGERY IN SCLC?
Georgios Stamatis
Thoracic Surgery, Ruhlandklinik/University Essen, Essen/Germany

The role of surgical treatment in the management of patients with small-cell lung cancer (SCLC) remains controversial. Although in the past, two randomized studies have failed to show any survival benefit by adding surgery to chemotherapy, different retrospective and prospective investigations including the recently published studies using the database of Cancer Institute Surveillance Epidemiology and End Results (SEER), showed, that surgery offers a reasonable overall survival in a subset of patients with SCLC stage I and II disease. Two important recommendations have been introduced regarding the histology of SCLC as a high grade aggressive neuroendocrine tumor and the use of TNM classification in staging of SCLC and in clinical trials. Patient's selection is important including extensive radiologic staging and biopsy of the mediastinal nodes. The use of PET scanning is likely to improve the accuracy of staging. Surgery can be performed with a curative intent in patients with SCLC and stage I or II disease or for the evaluation of response after chemotherapy. Weksler has used the SEER database and analyzed the outcomes of 5366 patients with SCLC stage I and II from 1988 to 2007. The surgical treatment was performed in 895 patients (25.1%); the median survival was 34 months in the surgical group versus 16 months in the nonsurgical group. In a similar report by Yu and colleagues, 21% of the 5-year overall survival was 21.1%, but it was 50.3% for those patients who received a resection (65.7% after pneumonectomy and 33.7% after sublobar one).

This analysis confirmed the acceptable survival rates in a subset of patients with stage I SCLC. By primary surgery or after induction chemotherapy combined modality tumor resection should be undertaken. Adjuvant chemotherapy is recommended also for stage I patients; prophylactic cranial irradiation prolongs survival in those patients who achieve a complete or partial response to initial treatment. Under these new, the standard systemic treatment of patients with LB SCLC is PCI which remains the combination of platinum and etoposide. The following groups of patients could potentially benefit from surgical resection: a. Patients with small lesion unexpectedly identified as SCLC at the time of thoracotomy. b. Complete resection and systematic lymph node dissection is undertaken. c. Patients with mixed histology initial treatment should be chemotherapy to control the small cell component and after that surgery to control the non-small cell part of the tumor. d. For patients with initial failure to chemotherapy or patients with localized late relapse after treatment for pure small cell tumors salvage operations may be considered on individual basis. e. In patients with second primary small cell or non-small cell lung cancer who achieved cure from primary SCLC, surgery should be considered in the course of multiple systemic approach f. Patients with synchronous ipsilateral or bilateral small and non small cell tumors could be potential candidates for surgery in a diagnostic or therapeutic intention g. In selected patients with IBA N2 disease and complete histological regression of tumor tissue in the mediastinal lymph nodes after induction chemotherapy or chemoradiation therapy, surgery can improve local control and survival. Taking into account the tumor use in SCLC and the encouraging SEER results for patients submitted to on of surgery, a reconsideration of the role of surgery seems to be mandatory. Finally, to improve current management strategies for SCLC, surgeons should participate in the evaluation of SCLC patients together with oncologists and radiotherapists and common guidelines for indications and therapy concepts should be adopted. Interdisciplinary approaches should be employed in the context of controlled clinical trials.


Immunotherapy of Small Cell Lung Cancer Nevin Murray MD, British Columbia Cancer Agency, Vancouver, Canada. The general principles of cytotoxic chemotherapy for advanced SCLC and NSCLC have many similarities and have advanced minimally over the past two decades. (1) The success of cancer genomics research in changing the care of patients with NSCLC with a driver mutation suitable for targeted treatment has been a powerful incentive to discover such molecular targets in SCLC. Although comparative genomic profiling shows some similarities between SCLC and NSCLC, the abnormalities identified to date are mainly tumor suppressor genes. (2) These loss-of-function alterations do not provide the clear opportunity for rapid clinical translation afforded by an activating mutation in a known receptor tyrosine kinase. A considerable number of targeted agents have already been tried in SCLC clinical trials without notable success. (3) In contrast, there is a growing body of evidence for immunotherapy as a promising new treatment for both SCLC and NSCLC. Immuno-therapy investigated for SCLC includes interferon, vaccines, antibody-drug conjugates and immune checkpoint inhibitors. Interferon and vaccines have been studied in phase I and II trials without sufficient activity to change practice. Although preliminary, the data emerging from trials of antibody-drug conjugates and immune checkpoint inhibitors has generated more excitement and are the focus for this abstract.

Antibody-Drug Conjugates (ADC) The components of an antibody-drug conjugate include an antibody directed at a defined antigen on cancer cells, a linker, and a cytotoxic agent. This package represents an effective mechanism of improved therapeutic index. Rovaaltuzumab tesirine targets the Notch pathway with a monoclonal antibody portion directed against the cell surface epithelial antigen. (5) In a phase I/II clinical trial enrolling 33 evaluable SCLC patients with a median of 2.5 previous chemotherapies, the response rate was 14% in second-line testing. As of a phase IB multi-cohort study (KEYNOTE-028), pembrolizumab was evaluated among patients with relapsed SCLC with PD-L1 positive tumors. (9) Of the 135 SCLC patients screened, 37 (27%) had PD-L1 positive tumors. The response rate was 29% in 24 evaluable patients. The median duration of response was 29 weeks and durable responses were observed. There is an ongoing phase II study of this agent as maintenance therapy after the completion of standard first-line therapy in extensive stage disease. A phase I trial is evaluating pembrolizumab with concomitant chemoradiation. Adverse events associated with checkpoint inhibitors is greater with CTLA-4 compared with the PD-1 antibody combination but were generally manageable. The proportion of patients becoming refractory for toxicity was usually less than 10%. The literature contains anecdotes of autoimmune syndromes such as lupus or pericarditis. Immune para-neoplastic syndromes are expected in a small proportion of patients with SCLC and an increase in their occurrence with immunotherapy requires close monitoring. Without sufficient activity to change practice. Although preliminary, the data emerging from trials of antibody-drug conjugates and immune checkpoint inhibitors has generated more excitement and are the focus for this abstract.

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cancers. The histopathological classification distinguishes thymomas from thymic carcinomas. Thymomas are further subdivided into different types (so-called A, AB, B1, B2, and B3) based upon the atypia of tumor cells, the relative proportion of the associated non-tumoral lymphocytic component, and resemblance to the normal thymic architecture. Thymic carcinomas are similar to their extra-thymic counterpart, the most frequent subtype being squamous cell carcinoma. The management of thymic epithelial tumours is a paradigm of multidisciplinary collaboration. The treatment strategy is primarily dependent on the histological type of the tumor. Complete resection is deemed not to be achievable upfront based on imaging studies, what is the case in Masaoka-Koga stage III/IVA tumors (classified as stage IIIA/IIIB/IVA in the 2015 IASLC-ITMIG TNM proposed system), after a biopsy is performed, primary induction chemotherapy is administered, part of a curative-intent strategy integrating subsequent surgical exploration or radiotherapy. Cases not eligible for local treatment receive definitive chemotherpay. Primary induction chemotherapy is then standard in non-resectable advanced thymic epithelial tumors. Cisplatin-based combination regimens should be administered; combinations of cisplatin, adriamycin, and cyclophosphamide, and cisplatin and etoposide are the most usually used. Primary chemoradiotherapy with platins and etoposide is an option, especially for thymic carcinomas. Usually 2-4 cycles are administered before imaging is performed to reassess resectability of the tumor. Surgery should be offered to patients for whom complete resection is thought to be ultimately achievable, or because of poor performance status or co-existent medical condition, definitive radiotherapy is recommended part of a sequential chemoradiotherapy strategy. Combination with chemotherapy (including cisplatin, etoposide chemotherapy and a total dose of radiation of 60 Gy) may be considered as well. Chemotherapy should be offered for patients with advanced, non-resectable, non-irradiable or metastatic (stage IVB) thymic epithelial tumor to improve tumor-related symptoms. The aim is to improve tumor-related symptoms through obtention of tumor response, while prolonged survival is uncertain. Cisplatin-based combination regimens should be administered. No randomized studies have been conducted, and it is unclear which regimens are best. Multagent combination regimens and anthracycline-based regimens appear to have improved response rates compared to others, especially the etoposide, ifosfamide and cisplatin combination. Combinations of cisplatin, adriamycin, and cyclophosphamide is preferred. Combination of carboplatin and paclitaxel is an option for tumor resection. Surgery or radiotherapy is possible in case of a clinical non-resectable condition. The choice of agents may be based on selected cases with unknown survival benefit. Recurrences of thymic epithelial tumors should be managed according to the same strategy as newly diagnosed tumors. Complete resection of recurrent lesions represents a major predictor of favorable outcome, and surgery is then recommended in case of resectable lesion. In case of non-resectable lesions, hence, several consecutive lines of chemotherapy may be administered when the patient presents with tumor progression. The re-administration of a previously effective regimen has to be considered, especially in case of previous response, late occurring recurrence, or relapse after surgery or radiotherapy, a patient in a good medical condition and not having received cumulative doses precluding the safety delivery of at least 3 additional cycles. Preferred regimens for second-line treatment include carboplatin plus paclitaxel, and paclitax and etoposide; capecitabine plus gemcitabine is an option. These regimens were evaluated in dedicated phase II trials, and one treatment line (gemcitabine and oxaliplatin) was reported as effective and well tolerated in patients with thymoma, and currently, partial resection of the thymus by VATS seems to be offered as the single modality treatment in advanced, non-resectable, non-irradiable or metastatic (stage IVB) thymic epithelial tumors.}

**EDIS: THYMIC MALIGNANCIES: UPDATE ON TREATMENT**

**EDIS.03 SURGERY OF THYMIC MALIGNANCIES**

Meisoshin Okumura

General Thoracic Surgery, Osaka University Graduate School of Medicine, Suita, Japan

Thymic epithelial tumors

Thymic epithelial tumors are the most common malignancy among mediastinal tumors according to Japanese thoracic surgery survey (1). Surgical resection is generally the treatment of choice for patients with thymic epithelial tumors. Thymic epithelial tumors are classified into thymoma, thymic carcinoma (TC), and thymic neuroendocrine carcinoma (TNEC). Retrosternal surgical database of Japanese Association for Research of the Thymus (JART) revealed that recurrence free 10-year survival after macroscopic complete resection was 58% in thymoma, 51% in TC and 14% in TNEC. The thymoma was classified mainly into 5 pathological subtypes, WHO type A, AB, B1, B2 and B3. Pathological subtype of thymoma has been shown to reflect the oncological behaviors, and post-operative recurrence rate increases in this order. JART database study revealed that nearly 3 quarters of thymoma surgical cases have Masaoka Stage III or IV disease at the moment of choice for thymic epithelial tumors. High-risk thymoma is treated by surgical resection, a considerable portion of TC is judged unresectable at initial presentation. TNEC often has nodal involvement. Initial resection is indicated when clinical diagnosis is a thymic epithelial tumor with Masaoka stage I or II. The standard procedure is extended thymectomy through median sternotomy even for tumors with Masaoka stage I or II disease because of the possibility of post-thymectomy myasthenia gravis, intrathymic metastasis and multiple foci of tumor. JART database study, however, revealed that recurrence rate in thymoma with T1N0M0 by UICC was not significantly different between subtypes, and recurrence free survival in thymoma was (1.4%) and thymomectomy (2.8%) (p = 0.192) (2). Furthermore, systematic dissemination of mediastinal lymph nodes is not supposed essential in thymoma because incidence of nodal involvement is negligible. Advancement in video-assisted thoracic surgery (VATS) has prompted endoscopic operation also for thymoma, and currently, partial resection of the thymus by VATS seems accepted for less-invasive thymoma when myasthenia gravis is not associated, but careful observation by annual examination by CT scan is recommended after partial thymectomy. Highly invasive thymomas should be treated by preoperative induction chemotherapy to reduce the tumor size. Pathological diagnosis by biopsy is required because chemotherapy is usually not indicated for patients with invasive thymoma and TC. Resection of the pericardium, lung, great vessels, and thoracic wall is sometimes required. JART database study revealed that invasion of the thoracic wall was the independent factor of recurrence and complete resection. (3) Even subtotal resection sometimes results in long-term survival. If complete resection is not achieved, radiotherapy is supposed to control the remaining tumor. Surgery for thymoma with pleural or intrapericardial dissemination can be indicated. JART database study revealed that the number of the disseminated lesions is a prognostic factor and many patients with less than 3 lesions have been cured. (4) Surgical procedure varies from partial pleurectomy to extrapleural pneumonectomy with resection of the primary lesion. The recommended procedure depends on the spread of disseminations. Although intrapericardial implantation is commonly thought to be hard to resect, resection can be achieved in some cases because thymomas usually do not invade into the heart muscle severely. Preoperative chemotherapy is supposed to enable complete resection of intrapericardial implants through reduction of the tumor volume. Most of the hemogenatous metastases of thymoma occur in the lung probably because the neoplastic cells can directly enter the blood stream through thymic veins. Surgical treatment for thymomas with lung metastasis is

**Keywords:** Thymoma, Thymic carcinoma

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feasible, but indication of surgery for thymoma with extrathoracic distant metastasis should be determined carefully. Recurrence often occurs on the pleural surface followed by the lung metastasis. Surgical resection of the recurrent lesions in the intrathoracic cavity is generally thought to contribute to survival. (5) Preoperative induction therapy is almost mandatory in highly invasive TC and poorly-differentiated NEC. Concurrent chemoradiotherapy is effective in reducing the tumor size. Resection and reconstruction of even the ascending aorta under cardiopulmonary bypass can be attempted. Systematic mediastinal and cervical lymph node dissection is recommended because of high incidence of nodal involvement.

Malignant germ cell tumors (GCT)

Malignant GCT is a highly aggressive neoplasm arising in young males. Chemotherapy is recommended without pathological diagnosis when serum tumor marker is extraordinarily elevated. In case of non-seminomatous GCT, complete resection of the tumor after normalization of tumor marker value by chemotherapy should be achieved, or otherwise, tumor recurrence is highly possible. Resection and reconstruction of the great vessels under cardiopulmonary bypass is often necessary.

Liposarcoma

Mediastinal liposarcoma is a rare neoplasms and sometimes appears as a huge tumor. This neoplasm is supposed to be resistant to chemotherapy, and complete surgical resection is required. Local recurrence occurs frequently because obtaining safe surgical margin is difficult. Radiotherapy could be a treatment of choice for recurrent tumors.

Lymphoid malignancies

Role of surgery is limited. Surgical biopsy is sometimes required when ML is suspected by imaging and high value of serum sIL-2 receptor. When tumor remains after chemotherapy, surgical resection is sometimes indicated. Low-grade malignancy including MALT and Castleman’s disease can be exceptionally treated by initial surgery.

References


Keywords: Thymic neuroendocrine carcinoma, Thymoma, Malignant germ cell tumor, Thymic carcinoma

RT is an excellent treatment option for patients with unresectable thymic malignancies. While most thymic tumors are resectable, a subset of patients is technically or medically inoperable, due to invasion of critical structures or comorbidities. In general, thymic malignancies are radiosensitive, allowing for long-term local control rates. Palliative RT should be considered even in the recurrent or metastatic setting. Image-guided hypofractioned ablative RT may be used for oligometastatic disease as an alternative to surgical resection and has been shown to be a highly effective treatment modality with >90% long-term local control rates and minimal morbidity. Conventional palliative RT is an important modality to improve quality of life by alleviating pain, treating SVC syndrome, airway compression and other symptoms. Modern radiation therapy techniques such as 3D conformal radiation therapy or intensity-modulated radiation therapy should be used to minimize morbidity from treatment. Proton therapy may have advantages in certain clinical scenarios and is currently under investigation.

Keywords: ADJUVANT, radiation therapy, Thymic malignancies
SCIENTIFIC SESSIONS

SESSION SC01: STAGING BEFORE AND AFTER INDUCTION THERAPY FOR N2 DISEASE
MONDAY, DECEMBER 5, 2016 - 11:00-12:30

SC01.01 THE IMPORTANCE OF MEDIASTINAL DOWN-STAGING DURING INDUCTION THERAPY OF N2 DISEASE
Paul De Leyn¹, Herbert Decaluwe¹, Christophe Dooms¹, Johan Vansteenkiste²
¹Thoracic Surgery, University Hospital Leuven, Leuven/Belgium; ²Respiratory Oncology, University Hospital KU Leuven, Leuven/Belgium.

Patients with preoperative pathological proven N2 disease have a dismal prognosis after surgery. Neoadjuvant chemotherapy or chemoradiotherapy is a therapeutic option that is usually patients with baseline resectable stage IIA-N2 non-small cell lung cancer. Mediastinal downstaging is an important prognostic factor for long term survival. Different restaging techniques are available. The mediastinum can be restaged by CT scan, mediastinoscopy, VATS, PET-CT and EBUS-EUS fine needle aspiration. In primary staging, CT scan has a sensitivity of 65%, a specificity of 75% and an accuracy of 71%. In mediastinoscopy, the sensitivity is 78% and the specificity is 81%. PET-CT has a sensitivity of 77% and a specificity of 88% (3). In primary staging, mediastinoscopy is technically feasible, but inaccurate due to severe adhesions and fibrosis. The sensitivity to detect residual mediastinal lymph node involvement was only 26.8% with an accuracy of 58.3%. Minimally invasive endoscopic procedures like endobronchial ultrasound with transbronchial needle aspiration are currently the gold standard for preoperative staging. However, endobronchial ultrasound with transbronchial needle aspiration is not the gold standard for CT scan in restaging the mediastinum is also. In a study of a Spanish study of 24 patients who underwent neoadjuvant chemotherapy for N2 non-small cell lung cancer, staging was performed by CT scan and mediastinoscopy (1). The sensitivity of CT scan was 69%, a specificity of 75% and an accuracy of 78%. In a prospective study of 93 patients who were restaged by integrated PET-CT after induction chemoradiotherapy, repeat PET-CT was found to be more accurate than CT alone for pathological stages. However, there were 4 false negative and 33 false positive CT scans. In a study performed in a prospective single center study, mediastinoscopy and PET-CT were evaluated in a prospective single center study and repeated mediastinoscopy and PET-CT after induction chemotherapy were performed for mediastinal staging in N2 disease. PET-CT had a sensitivity of 77% and a specificity of 88% (3). Repeat mediastinoscopy, technically much more difficult than the first procedure, offers the advantage of providing histological evidence of response. Although some centers obtained good results (4), most surgeons will accept that mediastinoscopy is diagnostically difficult and often incomplete. We performed a prospective study to evaluate the accuracy of mediastinoscopy and PET-CT in restaging the mediastinum after mediastinoscopy proven N2 disease (3). Malignant mediastinal lymph node involvement was defined as lymph node level 3.6 per patient biopsied. In our experience, mediastinoscopy was technically feasible, but inaccurate due to severe adhesions and fibrosis. The sensitivity to detect residual mediastinal lymph node involvement was only 26.8% with an accuracy of 58.3%. Minimally invasive endoscopic procedures (endobronchial ultrasound with transbronchial needle aspiration) are currently the gold standard for preoperative staging. However, endobronchial ultrasound with transbronchial needle aspiration is not the gold standard for CT scan in restaging the mediastinum in N2 disease.

REFERENCEs

3. Decaluwe H, Vansteenkiste J, Deweere W, Verbeken E, Dooms C, et al. Mediastinoscopy with nodal dissection should be performed. Also repeat PET-CT should be performed. If the mediastinum is at least level 3.6 per patient biopsied. In our experience, mediastinoscopy was technically feasible, but inaccurate due to severe adhesions and fibrosis. The sensitivity to detect residual mediastinal lymph node involvement was only 26.8% with an accuracy of 58.3%. Minimally invasive endoscopic procedures (endobronchial ultrasound with transbronchial needle aspiration) are currently the gold standard for preoperative staging. However, endobronchial ultrasound with transbronchial needle aspiration is not the gold standard for CT scan in restaging the mediastinum in N2 disease.

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SC01: STAGING BEFORE AND AFTER INDUCTION THERAPY FOR N2 DISEASE
MONDAY, DECEMBER 5, 2016 - 11:00-12:30

SC01.04 THE ROLE OF MEDIASTINOSCOPY IN INDUCTION THERAPY OF N2 NSCLC
Sergi Call
Department of Thoracic Surgery, Hospital Universitari i Politecnic de Terrassa, Spain

Rationale for restaging after induction therapy Persistent mediastinal nodal involvement after induction therapy is an independent prognostic factor associated with poor prognosis [1]. Based on the results of two phase III clinical trials on multimodality treatment for pathologically proven N2 non-small cell lung cancer (NSCLC) [2,3], patients with persistent mediastinal involvement do not benefit from surgical resection in terms of survival. The assessment of an objective response after induction therapy continues to be a diagnostic challenge. For this reason, the use of mediastinoscopy as a criterion to select patients for surgery requires a reliable restaging method to predict pathologic stage before lung resection. Algorithm for mediastinal restaging The European Society of Thoracic Surgeons guidelines for preoperative mediastinal nodal involvement for NSCLC recommend histological or videoassisted mediastinoscopic confirmation of objective response after induction therapy. This confirmation can be done with ultrasound-guided endoscopic techniques. However, the use of an invasive surgical technique is still recommended when the results of endoscopic procedures are negative [4]. The role of mediastinoscopy Mediastinoscopy in restaging can be performed in the following situations: 1) after induction therapy with no pretherapeutic invasive diagnosis; 2) after induction therapy with mediastinal histological confirmation by endoscopic techniques; 3) after induction therapy preceded by staging mediastinoscopy. In this case, mediastinoscopy is a reoperation: a mediastinoscopy. The use of first mediastinoscopy for restaging is addressed in a small series [5]. In this article, a negative predictive value (NPV) of 90% with a prevalence of ypN2 of 46% were reported. Theoretically, this approach could be a good strategy to perform an easier and safe mediastinoscopy due to the absence of adhesions in the mediastinum. Mediastinoscopy (remS) is a technique that does not differ much from a conventional mediastinoscopic technique. However, remS is technically more demanding because of peritracheal adhesions, resulting in a lower accuracy in comparison with the first procedure. The main goal of this procedure is to take new biopsies of those nodes that had been positive at first mediastinoscopy. Moreover, if it is technically feasible, other nodal stations should be reached to rule out subclinical progression of the disease. Although remS is not a common procedure, several authors have reported its feasibility and consistent results (see Table 1). In addition, its results do not seem to depend on the type of the induction therapy (chemotherapy or chemoradiation). The role of transcervical lymphadenectomy During the last decade, two new surgical staging procedures were developed: videoassisted mediastinoscopic lymphadenectomy (VAML) and transcervical extended mediastinal lymphadenectomy (TEMLA). The main difference between these procedures is that VAML is an endoscopic technique performed through a videomediastinoscope, and TEMLA is an open procedure assisted by a videomediastinoscope or a videothoracoscope, depending on the nodal station dissected. Both techniques imply the removal of all the lymph nodes of the explored nodal stations, allowing the identification of minimal nodal disease that is not identified on computed tomography (CT) or positron emission tomography (PET). Therefore, after a properly performed transcervical lymphadenectomy, the restaging of the mediastinum is unnecessary because there is no material left for a new biopsy. Focusing on the use of these procedures for restaging after induction therapy, only TEMLA has been validated on two retrospective studies conducted in the same institution. In the first series with 63 patients, the diagnosis of N2 disease after induction treatment was confirmed with invasive techniques in 27 patients (20 with endobronchial ultrasound [EBUS] and/or mediastinoscopy), and with CT in 36. Sensitivity, specificity and accuracy of restaging TEMLA were 95.5%, 100% and 98.3%, respectively [6]. In the second series with 176 patients treated with chemo- or chemoradiotherapy, the restaging values of endobronchial ultrasound (EBUS) and/or esophageal ultrasound (US) were comparable with those of TEMLA [78 patients]. There was a significant difference between EBUS/TEMLA and sensitivity (64.3% and 100%; p < 0.01) and NPV (82.1% and 100%; p < 0.01) in favor of TEMLA [10]. Regarding their use for primary staging, VAML and TEMLA represent a new paradigm. Firstly, transcervical lymphadenectomies could also be considered as a staging treatment because the mediastinum is staged and downstaged by these operations. Secondly, due to the fact that nodal restaging is unnecessary, new parameters should be used to select patients for lung resection after induction such as the stability of the primary tumor and the absence of extrathoracic disease based on the results of postinduction CT or PET. Finally, intraoperative pathologic staging of the remaining lymph nodes should confirm the absence of nodal involvement before proceeding with lung resection, especially if pneumonectomy is required. Conclusions In multimodality treatments for patients with stage IIIA(N2) tumors, pathologic restaging after induction therapy is essential to define the correct treatment for remaining adenopathy. However, the role of the induction treatment used or the intensity of the first mediastinoscopy. The role of transcervical lymphadenectomies in staging and restaging should be implemented in clinical practice and validated in future clinical trials. References 1. De Weale M, Soetikno R. 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Mediastinoscopy in restaging of lung cancer after induction therapy. J Thorac Cardiovasc Surg 2008;135:843-48. 10. Zielinski M, Hauer L, Hauer J, et al. Non-small-cell lung cancer restaging with transcervical extended mediastinal lymphadenectomy. Eur J Cardiothorac Surg 2010;37:778-80. 11. Zielinski M, Szulowsky A, Kolodziej M, et al. Comparison of endobronchial ultrasound and esophageal ultrasound with transcervical extended mediastinal lymphadenectomy for staging and restaging of non-small-cell lung cancer. J Thorac Oncol 2013;8:630- 6. Table 1. Staging values of the largest published series of mediastinoscopic restaging after induction therapy. Author Year N S NPV DA Stamatis et al. [7] 2005 160 0.74 0.86 0.92 De Weale et al. [1] 2008 104 0.71 0.73 0.84 Marra et al. [6] 2008 104 0.61 0.85 0.88 Call et al. [8] 2011 84 0.74 0.79 0.87 Abbreviations: N: number of patients; S: Sensitivity; NPV: Negative predictive value; DA: Diagnostic accuracy

Keywords: restaging, Mediastinoscopy, induction therapy

SC01.05 VIDEO-THORACOSCOPY FOR STAGING OF N2 NSCLC DURING INDUCTION THERAPY
Thomas D’Amico
Surgery, Duke Cancer Institute, Durham/NC/United States of America

The optimal strategy for patients with stage III non-small cell lung cancer (NSCLC) is not well-established and significant variation in practice exists across the United States and Europe. In the U.S., the majority of National

Keywords: lung cancer surgery, minimally invasive surgery, stage IIA
SC02.02 SURGICAL CHOICES FOR PATIENTS WITH MULTIFOCAL LUNG CANCER
Scott Swanson
Thoracic Surgery, Brigham and Women’s Hospital, Boston/United States of America

The Surgical Choices for Patients with Multifocal Lung Cancers Surgery for patients with multiple lung lesions is a growing domain. CT scans are obtained frequently and have high resolution such that any lesion in the lung that is 2 millimeters or larger can be identified. Also, it appears that multifocal lung lesions are more common now. At the same time, surgical technology (minimally invasive) has evolved so identifying and resecting small lesions is straightforward and associated with very little morbidity and pain. In most cases there is one lesion (primary lesion) that is more concerning and others that are smaller, less solid or relatively unchanged over time. Often a diagnosis of all of the lesions is not known at the time of surgical intervention and in many cases no diagnosis is known ahead of time. Thus, the surgeon must integrate many factors when operating on multifocal lung findings.

What are risk factors that the patient will have lung cancer, what are the patient’s co-morbidities and underlying lung function? When is it important to establish a pre-operative diagnosis? How important is it to resect all of the pulmonary lesions seen on CT scan? Will other therapy be needed? In general, our approach is to obtain a pre-operative diagnosis when possible if the surgery will be particularly challenging based on the location and number of the lesions and/or if the patient has very compromised lung function. The most important point is to anatomically resect the primary lesion; that nodule which is largest, most solid and/or growing the fastest. This will provide an excellent oncologic outcome and more readily permit other pulmonary intervention and in many cases no diagnosis is known ahead of time. Thus, the surgeon must integrate many factors when operating on multifocal lung findings.

The outcome of patients who had surgery for multiple lung cancers is generally quite good and not statistically different than the outcome for a solitary lung cancer. The patients in these series were highly selected. In most cases the pathology of these lesions is a mix between invasive adenocarcinoma (various subtypes), minimally invasive adenocarcinoma and adenocarcinoma in-situ. Whether mutations are identified is variable and does not seem to influence prognosis.

Use of adjuvant therapy depends on the completeness of resection, the nodal status and the molecular analysis of the resected tumors. In general, assuming no nodal involvement and complete resection of the lesions, no adjuvant therapy is recommended. In all cases close follow-up is mandatory with visits and frequent CT scans (2-3yr for 2 years then 1-2/year for 3 years then 1yr for life). Graph of Survival for patients treated by surgical resection for synchronous primary lung cancers.

Figure taken from: Finley et al. Journal of Thoracic Oncology. 2010. (ref 2)

References:
Mohiuddin K et al. Relationship between margin distance and local recurrence among patients undergoing wedge resection for small (<2 cm) non-small cell lung cancer. Journal of Thoracic and Cardiovascular Surgery. 2014.

SC02.03 SURGERY FOR GROUND GLASS OPACITY: SUBLOBAR RESECTION?
Shun-Ichi Watanabe
Thoracic Surgery, National Cancer Center Hospital, Tokyo/Japan

History of standard surgical procedure for lung cancer: In 1933, Graham reported the first successful pneumonectomy for a lung cancer patient, who survived for 18 years after surgery. In 1951, Cahen suggested that pneumonectomy with regional lymph node dissection should be a routine procedure for lung cancer in 1951. Then in 1960, Cahen reported the first 48 cases that successfully underwent lobectomy with regional lymph node dissection, which was called “radical lobectomy.” Since then, this procedure was universally accepted and has remained a standard surgery for lung cancer. As for sublobar resection, segmentectomy was initially used for the resection.
of localized bronchiectasis as reported by Churchill and Belsey (1939). In 1973, Jensik reported their 15-year successful experience of segmentectomy for localized bronchiectasis as reported by Churchill and Belsey (1939). In 1973, Jensik reported their 15-year successful experience of segmentectomy for localized bronchiectasis as reported by Churchill and Belsey (1939). In 1973, Jensik reported their 15-year successful experience of segmentectomy for localized bronchiectasis as reported by Churchill and Belsey (1939). In 1973, Jensik reported their 15-year successful experience of segmentectomy for localized bronchiectasis as reported by Churchill and Belsey (1939). In 1973, Jensik reported their 15-year successful experience of segmentectomy for localized bronchiectasis as reported by Churchill and Belsey (1939).
Introduction

Approximately 65 particle therapy facilities are in operation worldwide. Among them, only 10 have carbon-ion therapy (CIRT) facilities (5 in Japan, 2 in Germany, 2 in China, and 1 in Italy), and the remainder have proton therapy facilities. More than 37,000 patients were treated with proton therapy worldwide from 1954 to 2014, including 15,000 in 2014, 86% of which were treated with protons and 14% with carbon ions and other particles. (From the Particle Therapy Co-Operative Group: http://www.ptcog.ch/). The National Institute of Radiological Sciences (NIRS) Chiba, Japan, has been treating cancer patients with high-energy carbon ions since 1994. Most of the patients who have been cured of cancer worldwide with carbon ions were treated at NIRS (1). From NIRS’s data, the efficacy of CIRT for NSCLC has been suggested. Here those results are reviewed, and the issue of this modern technology is discussed. Characteristics of carbon-ion therapy CIRT has better dose distribution to tumor tissue, while minimizing surrounding normal tissue dose, compared with photon radiotherapy. Moreover, carbon ions have potential advantages over protons. They provide a better physical dose distribution due to lessened lateral scattering. Further, their higher relative biological effectiveness and lower oxygen enhancement ratio are desirable features for targeting radioresistant, hypoxic tumors. The difference between densely ionizing nuclei and sparsely ionising x-rays and protons offers further potential radiobiological advantages, such as reduced repair capacity, decreased cell-cycle dependence, and possibly stronger immunological responses. Carbon-ion therapy of early non-small cell lung cancer Surgical resection with lobectomy has been the standard treatment of choice for early-stage NSCLC. In a 2004 study of a Japanese lung cancer registry comprising 11,663 surgical cases, 20% of patients were 80 years of age and older with stage I NSCLC. Int J Radiat Oncol Biol Phys 2014; 55(suppl 1): i26–i27.

Keywords: proton therapy, lung cancer, clinical trials

SC03: ADVANCES IN RADIATION ONCOLOGY
MONDAY, DECEMBER 5, 2016 - 11:00-12:30

SC03.02 PROTON THERAPY OF LUNG CANCER
Jeffrey Bradley
Radiation Oncology, Washington University School of Medicine, St. Louis/United States of America

This session will focus on the use of proton beam radiation therapy for lung cancer. We will review the basic physics of proton beam therapy, why protons are different from photon-based radiation therapy, and the potential advantages of using proton beam therapy to treat lung cancer. We will review the current data about the use of protons, both published and unpublished, and provide updates on ongoing clinical trials testing proton therapy in lung cancer patients.

Keywords: protons, radiation therapy, lung cancer, clinical trials

SC03.03 CARBON-ION THERAPY OF LUNG CANCER
Yuko Nakayama
Department of Radiation Oncology, Kanagawa Cancer Center, Yokohama, Japan


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Keywords: carbon-ion therapy, non-small cell lung cancer, J-CROS

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SC04.02 MANAGEMENT OF RESISTANCE TO EGFR TYROSINE KINASE INHIBITORS
Tetsuya Mitsudomi
Thoracic Surgery, Kindai University Faculty of Medicine, Osaka-Sayama/Japan

Discovery of activating mutations of the EGFR gene in adenocarcinoma of the lung in 2004 opened the door to a new era for personalized therapy in thoracic oncology. Lung cancers with EGFR mutation are highly sensitive to EGFR tyrosine kinase inhibitors (TKI) such as gefitinib, erlotinib, or afatinib, resulting in significantly prolonged progression free survival compared with those treated with platinum doublet chemotherapy. However, acquired resistance inevitably develops usually after a median of 10~12 months. The mechanisms for this resistance have been extensively studied and can be classified into 1) target gene alteration, 2) activation of bypass/ accessory pathway, and 3) histologic transformation (Fig.).

The most common (50~60%) mechanism for acquired resistance to the EGFR TKI is a missense mutation at codon 790 of the EGFR gene resulting in substitution of threonine to methionine (T790M). This amino acid change reduces affinity between EGFR kinase and EGFR-TKI compared with that between EGFR-kinase and ATP, leading to reactivation of downstream signal pathways. L767S, L767F, and T790A are also known as secondary mutations that cause acquired resistance, but they are very rare. In these cases, cancer cells are still addicted to or dependent on EGFR pathway. Amplification of the MET gene which codes for a receptor of hepatocyte growth factor (HGF) was the first that was identified as a bypass track resistance mechanism against EGFR-TKI. Following this report, aberrant activation of other receptor tyrosine kinases such as HER2, HER3, AXL, IGF1R, have been reported. It is also shown that some ligands for the receptor tyrosine kinases such as HGF, FGF or IGF cause acquired resistance to EGFR-TKIs. Similarly, alteration of downstream molecule cause resistance. These molecules include BRAF, PTK7, JAK2, CRKL, DAPK, NF-κB, or PUMA. The third mechanism of acquired resistance is histologic transformation that includes small cell lung cancer transformation and epithelial-mesenchymal transition (EMT). Exact mechanisms of these histologic changes are not fully understood. However, AXIN, Notch-1, TGFβ pathway activation as well as down regulation of MED12 (Mediator Complex Subunit 12) have been proposed as mechanisms of EMT. Then, How are we able to cope with these resistance? For T790M gatekeeper mutations, the third generation EGFR inhibitors that selectively inhibit EGFR-T790M while sparing the wild-type EGFR are active. One of these drugs, osimertinib is already approved and gives a response rate of ~60% and progression free survival of ~11 months. Therefore, identification of T790M at the time of disease progression by rebiopsy is important. We have recently found that three other secondary EGFR mutations implicated in acquired resistance are also sensitive to osimertinib. Tumor resistance caused by activation of accessory pathways can be theoretically coped with by combination of the inhibitor of EGFR and involved molecules. However, because of rarity of each mechanism, there is no clear evidence whether these combination therapies will actually improve patient outcome. In other cases, cytotoxic chemotherapy is still an important strategy. According to the IMPRESS study, median progression free survival for patients without T790M who received cisplatin plus pemetrexed was ~5.4 months. Even with these strategies, cancer cells are smart enough to escape from the therapy using other mechanisms. Heterogeneities in terms of resistant mechanisms within a single patient become evident when specific therapeutic pressure persists. Therefore, we also need to have armamentarium that utilizes other mechanisms to cure lung cancer. Recent developments targeting immune checkpoints appear attractive in this respect. These mechanism-driven therapeutic approaches will convert this fatal disease into a more chronic disorder, and eventually into a curable disease with the least patient burden.

Keywords: Adenocarcinoma, EGFR, Resistance, T790M

SC04.03 SEQUENCING OF EGFR TYROSINE KINASE INHIBITORS
Keunchul Park
Div of HEM/ONC, Samsung Med Ctr, Sungkyunkwan Univ School of Med, Seoul/ Korea, Republic of

Treatment of EGFR-mutant (EGFRm) lung cancer with specific EGFR TKIs, such as gefitinib, erlotinib or afatinib, has opened the door to the precision medicine in the management of advanced non-small cell lung cancer with remarkable tumour shrinkage and improvement in progression-free survival (PFS) and quality of life compared to standard chemotherapy. Despite such a remarkable initial clinical response with EGFR TKIs in patients with EGFR+ NSCLC, however, the disease eventually comes back with the emergence of acquired resistance and median PFS is ~1 year. The most common mechanism of resistance is acquisition of the T790M gatekeeper mutation and the 3rd-generation EGFR TKIs (irreversibly inhibit mutant EGFR, esp. T790M), with sparing wild-type(WT) EGFR. There are several EGFR mutant specific inhibitors (EMSIs) under development including AZD9291, CO-1686, BIB42654, HM61713, ASP8273, etc.

All these third-generation EGFR TKIs have shown a promising early clinical efficacy in T790M(+) EGFR NSCLC patients with ORR of 60% and PFS of 9.6 – 10.3 months and appear to be well tolerated. Based upon these encouraging early results many confirmatory phase 3 trials (e.g., NCT02151981, NCT02322281) comparing to the standard chemotherapy in the 2nd-line setting are underway.

It is very tempting that one might like to move the 3rd-generation EGFR TKI to 1st-line setting. The development of the 3rd-generation agents as the first-line therapy for patients with EGFRm disease has already started. Recently AZD9291 demonstrated an encouraging clinical activity and a manageable tolerability profile in 1st-line: confirmed objective response rate of 77% (95% CI 64, 87) and mPFS of 19.3 months (investigator-assessed). Currently it is being compared with the 1st/2nd-generation EGFR TKI in the 1st-line setting. The Phase II FLAURA study (NCT02296125), comparing AZD9291 80 mg once daily versus current standard of care EGFR-TKIs for treatment-naive patients, is enrolling. Though the preliminary result in the 1L setting is quite provocative, extreme caution needs to be exerted since the currently available data are not mature enough to determine which agent is the best in its class and only from a small subset of patients.

Though it is hoped that the T790M-mediated resistance can be delayed or prevented by using the EMSIs in the TKI-naive setting, it is also possible that other less well known escape mechanisms might emerge. Given that ESMI works well after failing 1st/2nd-generation EGFR TKI it believe it seems to be a more reasonable approach to investigate if ESI in the TKI-naive setting is more effective than 1st/2nd-generation EGFR TKI followed by ESI when failing 1st/2nd-generation EGFR TKI with acquired resistance.

One of the biggest questions to emerge in the era of next-generation inhibitors that have activity against the basic driver oncogene is whether it makes sense to use this approach before the development of acquired resistance to prevent it from occurring in the first place. Can its use in the 1st-line(TKI-naive) setting prevent the development of acquired resistance and lead to a longterm control of the disease?

Considering the well-known genomic heterogeneity with its possible association with resistance to TKIs we need better understanding of the biology and resistance mechanisms to this class of new generation EGFR TKIs in order to develop better strategies for subsequent therapies to overcome the resistance including how to best sequence the available EGFR TKIs in the clinic as well as combination therapies.

It is fair to say that during the past few years we’ve clearly made another progress in the management of NSCLC patients with EGFRm, including those who failed previous EGFR TKIs. However, the currently available data are not mature enough to determine which agent is the best in its class, with the notable differences primarily related to toxicity and we’re not there yet and still lots of unanswered questions remain and further researches are warranted.
A considerable degree of discordance between such assays 4,6,7. "Liquid" biopsies side-by-side reveal inferior sensitivity of blood-based assays. Secondly, most studies comparing EGFR mutation detection in tumor and from validation studies conducted with tumor-derived DNA. In consequence, enables the study of comprehensive genomic biomarker panels in blood-development of more sensitive technologies and bioinformatic algorithms genomic biomarkers and treatment monitoring in advanced lung cancer. The mutations, such as EGFR T790M or the EGFR C797S, in circulating DNA 4,5. circulating in the blood from patients with EGFR-mutated lung cancers mutations can be detected by highly sensitive assay technology in free DNA tyrosine kinase, which have demonstrated superior progress-free survival and, in some instances, overall survival when compared to platinum-based chemotherapy in first-line treatment. Several studies have shown that EGFR mutations can be detected by highly sensitive assay technology in free DNA circulating in the blood from patients with EGFR-mutated lung cancers 1,2,3. Circulating EGFR-mutated DNA may drop below the level of detection in patients responding to EGFR-TKI, and persistence or reoccurrence of circulating EGFR-mutated DNA may associate with primary and acquired resistance 1,3. In addition, clonal evolution of EGFR-mutated lung cancers under EGFR-TKI therapy can be mirrored by the detection of gatekeeper mutations, such as EGFR T790M or the EGFR C797S, in circulating DNA 4,5. Hence, mutation analysis in circulating free DNA has been suggested as a clinically more feasible and less invasive method for detection of predictive genomic biomarkers and treatment monitoring in advanced lung cancer. The development of more sensitive technologies and bioinformatic algorithms enables the study of comprehensive genomic biomarker panels in blood-derived DNA, which cover a broader spectrum of actionable mutations in treatment-naïve patients and those with acquired TKI resistance. Currently, there are still several limitations to overcome. First, the predictive value of a mutation detected in blood-derived DNA cannot be simply extrapolated from validation studies conducted with tumor-derived DNA. In consequence, prospective clinical validation of blood-based biomarkers is mandatory. Secondly, most studies comparing EGFR mutation detection in tumor and "liquid" biopsies side-by-side reveal inferior sensitivity of blood-based assays. Also, there is a considerable degree of discordance between such assays 4,6,7. Thus, "negative" findings in circulating tumor DNA have to be confirmed by a second assay in tumor-derived DNA. Apart from inflating spending on molecular diagnostics, this may result in further treatment delays, which is hard to bear for patients in particular in the first-line setting. While these obstacles may be soon overcome by technological advances and evolving data from validation studies, "liquid biopsies" focusing on DNA and/or RNA will always miss out on the histopathological information that can be derived from a biopsy of a tumor or metastasis. In the era of immunomodulatory antibody therapy information of tumor-infiltrating immune and stromal cells as well as expression of biomarkers by specific cell populations or with spatial variation become increasingly important. Until this information cannot be reproducibly derived by novel assay technologies the detection of genomic biomarkers in blood-derived DNA will become a highly valuable, additive modality for specific scenarios of primary diagnosis and treatment monitoring.

**References**


**Keywords:** EGFR, biomarker, Genomics, Resistance

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**SESSION SC05: NOVEL DRUGS IN THORACIC CANCERS**

**MINDAY, DECEMBER 5, 2016 - 11:00:12:30**

**SC05.02 NOVEL CYTOTOXIC DRUGS IN LUNG CANCER**

Jean-Charles Soria  
Drug Development Department, Gustave Roussy, Villejuif/France

Even in the era of precision medicine and immunotherapy, cytotoxic chemotherapies remain an essential component of lung cancer treatment, both in resectable disease as well as in advanced/metastatic lung cancer. We have chosen to focus on 2 new cytotoxic compounds, which are likely to emerge as new players in the field of lung cancer management. One (named PM1183) has activity in small-cell lung cancer (SCLC), the other TAS-114 has activity in non-small cell lung cancer (NSCLC). PM1183 is a DNA-binding chemotherapy with a new mechanism of action. PM1183 acts as an inhibitor of transcription. Binding of PM1183 to CG-rich motifs, triggers sequential phosphorylation of Pol II and stalling of elongating Pol III. This leads to recruitment of the ubiquitin-proteasome machinery, RNA Pol II degradation, and recruitment of XPF, generation of DNA breaks and induction of apoptosis. PM1183 has been tested in a phase IIB trial in combination with doxorubicin. In the dose-finding part: recommended dose (RD) was defined at PM1183 4.0 mg flat dose (FD) or 2.0 mg/m2; DOX 50 mg/m2 both on day (D)1 every three weeks (q3w). Myelosuppression was dose-limiting (DLT). Compelling activity was observed during escalation phase. It was especially remarkable as 2nd line in SCLC patients: 5 of 7 evaluable pts (71%) had objective partial response (PR) as per RECIST v.1.1. In an expansion cohort of 20 patients, PM1183 and DOX showed outstanding clinical activity: 62% response rate, including 10% of CRs, as 2nd line treatment in SCLC patients. A randomized phase III trial testing PM1183 + DOX is planned and will compare this combination with topotecan or CAV. TAS-114 is a first-in-class oral deoxyuridine triphosphatase (dUTPase) inhibitor that acts as a modulator of the pyrimidine nucleotide metabolic pathway by blocking the conversion of 2 deoxyuridine-5'-triphosphate (dUTP) into 2-deoxyuridine-5'-monophosphate (dUMP), through reversible inhibition of dUTPase (gatekeeper protein), resulting in the enhanced incorporation of both uracil and fluorouracil into DNA. The activity of TAS-114, administered in combination with thymidine synthase (TS) inhibitors, 5-FU, S-1 or capecitabine, has been studied pre-clinically in various cancer cell lines and animal models. TAS-114 selectively inhibited dUTPase and showed a higher affinity than the substrates of dUTPase, dUTP and dUDP, inhibition constant values of TAS-114 were 0.13 pM and 0.10 µM, respectively. The antitumor effect of TAS-114 combined with 5-FU compared to that of 5-FU alone was investigated in vivo using a xenograft mouse model with NSC-H2228 (human NSCLC). Both regimens were administered orally (TAS-114: 600 mg/ kg/day and S-1: 8.3 mg/kg/day vs S-1: 8.3 mg/kg/day through day 1 to 28) and resulted in relative tumor volumes of 1.61% vs 3.04%, p<0.01, inhibition rates of 52.7% vs 10.8%, and body weight changes of 6.8% vs 3.3%, respectively. A phase I clinical study of TAS-114 and S-1 combination treatment is currently ongoing to investigate the safety and to determine the maximum-tolerated dose (MTD) and recommended dose (RD) in patients (pts) with advanced refractory solid tumors. TAS-114 and S-1 are administered orally twice a day.

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**SC04.04 LIQUID BIOPSIES FOR DYNAMIC MONITORING OF EGFR MUTATIONS IN LUNG CANCER**

Martin Schuler  
West German Cancer Center, University Hospital Essen, Essen/Germany

Somatic mutations clustering in exons 18 to 21 of the EGFR gene characterize distinct lung cancer biology. Patients with metastatic EGFR-mutated lung cancer are exquisitely sensitive to targeted agents inhibiting the EGFR tyrosine kinase, which have demonstrated superior progress-free survival and, in some instances, overall survival when compared to platinum-based chemotherapy in first-line treatment. Several studies have shown that EGFR mutations can be detected by highly sensitive assay technology in free DNA circulating in the blood from patients with EGFR-mutated lung cancers 1,2,3. Circulating EGFR-mutated DNA may drop below the level of detection in patients responding to EGFR-TKI, and persistence or reoccurrence of circulating EGFR-mutated DNA may associate with primary and acquired resistance 1,3. In addition, clonal evolution of EGFR-mutated lung cancers under EGFR-TKI therapy can be mirrored by the detection of gatekeeper mutations, such as EGFR T790M or the EGFR C797S, in circulating DNA 4,5. Hence, mutation analysis in circulating free DNA has been suggested as a clinically more feasible and less invasive method for detection of predictive genomic biomarkers and treatment monitoring in advanced lung cancer. The development of more sensitive technologies and bioinformatic algorithms enables the study of comprehensive genomic biomarker panels in blood-derived DNA, which cover a broader spectrum of actionable mutations in treatment-naïve patients and those with acquired TKI resistance. Currently, there are still several limitations to overcome. First, the predictive value of a mutation detected in blood-derived DNA cannot be simply extrapolated from validation studies conducted with tumor-derived DNA. In consequence, prospective clinical validation of blood-based biomarkers is mandatory. Secondly, most studies comparing EGFR mutation detection in tumor and "liquid" biopsies side-by-side reveal inferior sensitivity of blood-based assays. Also, there is a considerable degree of discordance between such assays 4,6,7. Thus, "negative" findings in circulating tumor DNA have to be confirmed by a second assay in tumor-derived DNA. Apart from inflating spending on molecular diagnostics, this may result in further treatment delays, which is hard to bear for patients in particular in the first-line setting. While these obstacles may be soon overcome by technological advances and evolving data from validation studies, "liquid biopsies" focusing on DNA and/or RNA will always miss out on the histopathological information that can be derived from a biopsy of a tumor or metastasis. In the era of immunomodulatory antibody therapy information of tumor-infiltrating immune and stromal cells as well as expression of biomarkers by specific cell populations or with spatial variation become increasingly important. Until this information cannot be reproducibly derived by novel assay technologies the detection of genomic biomarkers in blood-derived DNA will become a highly valuable, additive modality for specific scenarios of primary diagnosis and treatment monitoring.

**References**

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**Keywords:** EGFR TKI, Resistance, Sequence
Abstracts

SC05.03 NOVEL TYROSINE KINASE INHIBITORS IN LUNG CANCER
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The invited talk will firstly talk about the recent advances in novel TKIs overcoming resistance during EGFR-TKI and ALK-TKI treatment. Afterwards, several novel TKIs with CNS penetration that may substantially change the prognosis of patients with brain metastases will be discussed. Finally, we will take an overview about targeted therapy against rare and novel, potentially drugable oncogenes during preclinical settings or early-stage clinical trials. As we know, the presence of EGFR activating mutations and ALK chromosomal rearrangements with corresponding tyrosine kinase inhibitors (TKIs) have revolutionized the treatment strategies of patients with non-small cell lung cancer (NSCLC) [1, 2]. Although tremendously initial response and manageable toxicity profiles, however, acquired resistance inevitably develops after approximately 1 year treatment with EGFR-TKIs (erlotinib and gefitinib) and ALK inhibitor (crizotinib). Encouragingly, third-generation EGFR-TKIs including AZD9291, C06186 and HM61731 have showed striking efficacy overcoming acquired resistance driven by T790M secondary mutations [3]. In patients who get acquired resistance to first-generation EGFR-TKIs with T790M mutations, the objective response rate (ORR) of AZD9291 was 61% and minimal progression-free survival (PFS) was 9.7 months (4). Other novel third-generation EGFR-TKIs such as ASP8274, EG818, PF-06747775 and avitinib are also being investigated in early-stage clinical trials and the survival and safety data will be released in the near future. Another promising novel EGFR-TKI, namely AZD3759 has showed promising response in patients with brain metastases and leptomeningeal disease, a major case leading to treatment failure. In BLOOM study, 11 out of 21 patients with measurable brain metastases and heavily pre-treated progressed both extracranially and intracranially had tumor shrinkage in the brain at dose ≥30mg BID. Recently, EAB045, an EGFR allostERIC inhibitor, in combination with cetuximab exhibit antitumor activity in mouse models of lung cancer driven by L858R/ T790M/C797S, a common resistant mechanism of AZD9291 [5]. Meanwhile, second-generation ALK inhibitors (ceritinib, alectinib and brigatinib) have entered clinical applications for NSCLC patients with ALK rearrangements after failed crizotinib and third-generation ALK inhibitors (lorlatinib and AP3026) are also being evaluated in clinical trials overcoming known ALK resistant mutants [6, 7]. In patients who progress on crizotinib, the ORR and PFS of brigatinib at 180 mg was 54% and 12.9 months. Lorlatinib, a third-generation ALK inhibitor, also demonstrated robust clinical activity in ALK-rearrangement patients with NSCLC. The ORR in 57% in patients who received 1 prior ALK-TKI and 42% in patients who received ≥2 prior ALK-TKIs. On the other hand, with the development of high-throughput sequencing, called next-generation sequencing (NGS) and genomic technologies, more novel molecular targeted therapy has become available. MET 14 exon 14 skipping mutations have been identified as potential therapeutic targets and simultaneously analyzing hundreds of molecular alterations have turned out reality with limited tumor tissues. In the recent years, the emergence of numbers of oncogenic drivers other than EGFR mutations and ALK rearrangements has divided NSCLC into many distinctive subtypes amenable to corresponding targeted therapy, including ROS1 rearrangement, RET rearrangement, BRAF V600E mutations, HER2 mutations and MET 14 exon skipping mutations et al. For instance, dabrafenib either as monotherapy or in combination with MEK inhibitor (trametinib) has displayed promising antitumor activity and manageable safety profile in patients with BRAF V600E mutations [9, 10]. In 57 previously treated metastatic NSCLC patients with BRAF V600E mutations, 63.2% patients (36/57) achieved an overall response [9]. Other cancers harboring novel molecular targets maybe serving as oncogenic drivers including mutations in HER2 (neratinib and pyrotinib) and PI3KCA (BKM120 and GDC0941), ROS1 (entrectinib, foretinib and lorlatinib), RET (XL184) and NTRK (entrectinib, rofiglitinib and OMS1776) are being evaluated either in preclinical settings or early-stage clinical trials. Recently, GDC0941 was investigated in 2 non-small cell lung (NSCLC) pts, 1 pancreas pt and 1 colorectal cancer patient to date. Amongst 6 evaluable NSCLC pts to date, there was an overall response rate of 33% (2/6) with 2 confirmed PR and a disease control rate of 100% (6/6). Pharmacodynamics analysis performed on patient tumor specimens treated at MTD indicated TAS-114 target engagement by reductions in the amount of intra-tumoral dUMP, a “surrogate” metabolite indicative of dUTPase inhibition, following TAS-114/S-1 combination as compared to S-1 alone administration. When TAS-114 is administered in combination with S-1, an additional cytoidal antitumor effect to TTP depletion by T3 inhibition is expected as TAS-114 inhibits a gatekeeper protein, thereby allowing increased DNA incorporation of both uracil and 5-FU resulting in DNA damage.

Keywords: new cytotoxics, small-cell lung cancer, non-small cell lung cancer

SC05.04 LUNG CANCER VACCINES: AN UPDATE
Elisabeth Quoix
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Treatment of small-cell lung cancer (SCLC) has not been modified since decades: and consists in a chemotherapy (CT) with platinum-etoposide +/- concurrent radiotherapy (RT) and prophylactic cranial irradiation in case of (partial)complete response to both therapy (SCLC). First-line platinum-doublets (docetaxel, pemetrexed, gemcitabine, irinotecan) represents 85% of all lung cancers, and around 50% are metastatic at presentation. Systemic treatment (platin-based doublets) has been implemented for stage IV NSCLC but also for locally advanced and early stages as (neo)adjuvant therapy to surgery or RT. By the end of the XXth century, a plateau has been reached in the stage IV disease with similar results whatever the drug used in conjunction with platin-salt. Since the beginning of the XXIst century there have been tremendous innovations in the systemic treatment of NSCLC. First, advancement of bevacizumab to CT for stage IV non-squamous cell carcinoma and the use of maintenance therapy have led to an improvement in median survival time (MST) exceeding now one year. Second, targeted therapies proved to be of major interest for patients with EGFR activating mutations leading to a MST-2 years. Other targets of interest have been such as ALK and ROSI translocations, V600E BRAF mutations leading to prolonging survival with appropriate treatments. Third, immunotherapy: the immune checkpoint blockers which aim at enhancing a tumor specific T-cell response directed against tumor-associated antigens and abrogate the immune tolerance and the therapeutic vaccines designed to induce or amplify an immune response directed against tumor-associated antigens (TAA). The immune checkpoint blockers in current development are anti CTLA4 monoclonal antibodies (ipilimumab), first used in the treatment of melanoma and now NSCLC, anti PD-1 (nivolumab, pembrolizumab) or anti PDL1 (avelumab, atezolizumab). All these molecules are now either at an advanced stage of development or already authorized (4). Therapeutic vaccines have already a long story beginning with Coley toxins at the end of the nineteenth century (5). The Coley’s toxins, cultures of...
streptococci) were infused in patients with bone and soft tissue sarcomas and some impressive regressions were observed. The hypothesis was that the immune reaction provoked by the infusion of the "toxins" present in the infectious material was able to destroy the tumoral cells. However, due to the reluctance of doctors to administer dangerous bacterial culture and the appearance of novel treatments of cancer (CT and RT), the Coley's toxin approach has been abandoned although numerous articles were devoted to this subject (6). Non specific vaccines using example BCG to stimulate innate immunity have been disappointing as well in SCLC (7,8) and NSCLC (9).

Specific immunotherapy aims at the stimulation of adaptive immunity against the vaccine components and thus induces or amplifies an immune response against TAA. These vaccines are either peptides (Tecmotide, MAGE-A3), cellular vaccines (Belagenpumatucel-L) or vaccines using viral vector (TG4010). Tecmotide and TG4010 are MAGE-A3 antigen-specific immunotherapy. MUC1 is expressed at the apical surface of mucin-secreting normal epithelial cells of various tissues and can be overexpressed and aberrantly glycosylated in some tumors and thus is an attractive target for immunotherapy. Tecmotide is a liposomal vaccine. In a randomized phase II trial (10), 171 NSCLC patients who were not progressing after induction CT or CT-RT received subcutaneous tecmotide plus best supportive care (BSC) or BSC alone as maintenance therapy. Median survival time (MST) was longer in patients receiving tecmotide (17.2 vs. 13.0 months) but this did not reach statistical significance. As in a post hoc analysis the benefit appeared to be more evident in the subgroup of patients with high level of TrPAL. A phase IIB was then performed to confirm the role of the vaccine in this subgroup, there was a significant survival benefit in favor of tecmotide whereas in the sequential CT-RT subgroup, survival did not differ between the two arms. A similar study (13) was initiated in Asian people. This trial was prematurely terminated as the sponsor decided to discontinue program with tecmotide as the MAGE-A3 antigen was expressed in 76% in the placebo and in 35% of NSCLC. It is absent from normal tissues except for testis and placenta. This vaccine has been investigated in early stage of NSCLC as an adjuvant treatment. A randomized phase II study (14) compared the MAGE-A3 vaccine to a placebo in 182 patients operated of a stage IB or II NSCLC with the tumor exhibiting the MAGE-A3 antigen. The randomization was made on a 2:1 basis. The main objective was to compare the Disease Free Interval (DFI) defined as the time from resection to the date of recurrence (any type) or second primary lung neoplasm. Although there was a trend toward a numerically longer DFI in the MAGE-A3 vaccine group, the main objective was not met. Nevertheless, even if these trends were far not significant, these results appear promising to the sponsors and a phase III trial was launched (MAGRIT trial) with the same scheme (15). Unfortunately, the biggest trial ever performed with the inclusion of 2312 NSCLC patients is negative regarding as well the primary objective: disease-free survival (DFS) but also the secondary objective: survival of patients receiving adjuvant chemotherapy or other subgroups. Belagenpumatucel-L is a vaccine comprising 4 transforming growth factor-β2-antigenic gene-modified irradiated allogeneic NSCLC cell lines. A randomized phase III trial (16) comparing this vaccine to a placebo was performed in a platinum-based CT for stage III/IV disease in non-progressing patients. This trial was negative with no difference in overall survival in PSF. However, in a prespecified multivariate analysis, there was an improved survival for patients who were randomized within 12 weeks after CT and for patients who received prior radiation therapy. TG4010 is a suspension of a recombinant modified vaccinia virus strain Ankara coding for the MUC1 TAA (Stimuvax*). Phase III study of adjuvant vaccination with Bec2/bacille Calmette-Guérin in responding patients with limited-disease small-cell lung cancer. J Clin Oncol 2005;23:6854–61. 11. Butts C, et al. Tecemotide (L-BLP25) versus placebo after chemoradiotherapy for stage III non-small-cell lung cancer (START): a randomised, double-blind, phase 3 trial. Lancet Oncol 2015;16:59–68. 12. Mitchell P, et al. 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SESSION SC06: NOVEL THERAPIES IN MALIGNANT PLEURAL MESOTHELIOMA AND THYMIC MALIGNANCIES

MONDAY, DECEMBER 5, 2016 - 14:30-15:45

SC06.03 INTRAOPERATIVE THERAPIES IN MALIGNANT PLEURAL...
MESOTHELIOMA
Isabelle Opitz
Division of Thoracic Surgery, University Hospital Zurich, Zurich/Switzerland

The rationale of localized/intracavitary treatment is to eliminate microscopic residual disease (MRD) after macroscopic complete resection (MCRR) for mesothelioma patients. The advantage of the treatment is that local effects can be enhanced whereas systemic side effects of the therapeutic agents applied might be reduced. Several approaches have been investigated over the past decades in preclinical and clinical trials, such as intracavitary chemotherapy (ICTX), immunotherapy (iIT), photodynamic therapy (PDT) and gene therapy (iGT). Intracavitary chemotherapy (ICTX) has been studied after mesothelioma resection, not only after extrapleural pneumonectomy (EPP) but also after (extended) pleurectomy/decortication (eP/D). The main therapeutic agent used is cisplatin. In some trials hyperthermia was additionally added with the aim to enhance the penetration of cisplatin into tissues and maximize its cytotoxicity in tumor cells[1]. Hyperthermic intrapleural perfusion had a maximum tolerated dose of 225-250 mg Cisplatin/m² BSA[2]. The morbidity range from 13 to 85% and the mortality from 0 to 29%[2, 3]. Some complications are related to renal toxicity which was the dose limiting adverse event[2]. Median survival time ranges up to 33.5 months in low-risk MPM patients receiving hyperthermic intrapleural cisplatin chemotherapy following MCRR[4]. This treatment is only considered for well-designed clinical trials. In vivo preclinical model using intraperitoneal administration of cisplatin-mixed loaded to a fibrin carrier improved the local drug concentration and prolonged the exposure of tissue to high cisplatin concentration[5]. Our phase I dose escalation trial (INFLuence – Meso; see figure) has proven the safety of this treatment approach (manuscript in preparation). This treatment regimen is now being tested in a phase II trial (NCT01644994).

In addition to chemotherapy, other substances have also been tested for intracavitary treatment. Recently, Tada, et al. reported study plan for a phase I trial for intrapleural treatment with zolendronic acid, a third generation of bisphosphonates, in inoperable MPM, after having successfully proven the efficacy of zolendronic in a preclinical model[6]. Intrapleural immunotherapy (iIT) MPM is not a classical “immunogenic” Tumor. Intrapleural instillation of cytokines such as interleukin (IL)-2, interferon (IFN)-α and IFN-γ provided a good control of malignant pleural effusion (MPE) and MPM tumor response[7, 8]. To prolong exposure of IFNs, recent studies implemented immuno-gene therapy approach using adenoviral vector expressing human IFNs. Four out of 10 patients with MPM and metastatic pleural effusions showed stable disease following a single dose of intrapleural adenoviral vector expressing IFN-β[9]. Nevertheless due to rapid production of neutralizing antibody against adenovirus, no improvement of gene transfer efficacy was achieved after the second dose[10]. The same research group conducted a clinical trial assessing the safety of adenoviral-mediated IFN-β2b in combination with chemotherapy. Recent data from this trial showed that the treatment is well tolerated and 25% of patients had partial response[11]. An intrapleural treatment with re-directed T cells genetically engineered to express chimeric antigen receptor (CAR) that specifically recognizes tumor antigens is an attractive therapeutic option. A clinical phase I trial for intrapleural administration of fibroblast activation protein (FAP)-specific re-directed T cells is currently being conducted (NCT01722146). Photodynamic therapy (PDT) PDT is a light based cancer therapy. Most modern PDT applications involve three key components: a photosensitizer, a light source and tissue oxygen. The photosensitizing agent accumulates in tumor cells and is activated by light of a specific wavelength to produce reactive oxygen that mediates cellular toxicity. The tumor cells are killed through both apoptosis and necrosis and by damaging tumor vasculature. It may also induce inflammatory reaction capable of stimulating a tumor directed host immune response. The advantages of this treatment are that its efficacy is not influenced by chemo- or radio-resistance of tumor cells, that it can be repeated at the same site without compromising its efficacy and that it does not compromise the ability to administer other treatment modalities in patients with recurrent or residual disease. PDT should be combined with macroscopic complete resection due to limited depth of penetration. Localized inflammation and fluid accumulation after treatment can obscure the pleural cavity. PDT appears promising and may improve local control and potentially prolong survival in properly selected patients who are able to undergo MCR, with clinical outcomes appearing best when PDT is combined with lung-sparing definitive surgery[12]. Friedberg reported a median survival of 31.7 months (41.2 months in patients with epithelioid histological subtype), but the progression free survival was only 9.6 months[13]. Intracavitary gene therapy (iGT) Gene therapy is based upon transfer of genetic material, including complementary DNA, full-length genes, small interfering RNA or oligonucleotides into cells for therapeutic purposes. For sufficient gene delivery, adenovirus is the most widely used in clinical trials among a variety of viral and non-viral vectors. In addition to delivering cytokine expressing vectors or re-directed T cells (see iIT part), several different cancer gene therapy approaches are currently used including the so called suicide gene therapy where a gene product is transduced with a death encoding for an enzyme rendering tumor cells sensitive to a benign agent by converting the product to a toxic metabolite. The Herpes Simplex Virus 1-thymidine kinase (HSV1tk) gene encodes for an enzyme that converts ganciclovir, an antiviral drug, to its cytotoxic metabolite. Intrapleural adenovirus HSV1tk/ganciclovir administration was safe and two patients survived >6.5 years. Nevertheless, due to the fact that transgenes HSV1tk were only detected at the surface of tumor tissues, the authors suggested that the treatment efficacy may be a result of antitumor immune response stimulation[14]. MPM tumor genome is characterized by frequent mutations in tumor suppressor genes such NF2, BAP1 or p53, thus the delivery of tumor suppressor gene expressing vectors into tumor cells can serve as an attractive treatment approach. The delivery of adenovirus expressing p53 has been tested in clinical trials for lung cancer but did not show better clinical benefit over chemotherapy[15]. This may be due to limited transfection efficiency of the vector used. For these reasons therefore an improvement of transfection is still needed for the further development of gene therapy. References: 1. Sugarbaker, P.H., et al., Update on chemotherapeutic agents utilized for perioperative intrapleural chemotherapy. Oncologist, 2005. 10(2): p. 112-22. 2. Richards, W.G., et al., Intrapleural chemotherapy for the management of malignant pleural mesothelioma and metastatic pleural effusions. J Clin Oncol, 2001. 19(5 Pt 1): p. 4456-66. 10. 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Keywords: malignant pleural mesothelioma, intracavitary chemotherapy, Intracavitary Immunotherapy, photodynamic therapy

SC06.04 IMMUNOTHERAPY OF MALIGNANT PLEURAL MESOTHELIOMA AND THYMIC MALIGNANCIES: THE END OF THE BEGINNING?

Jan Van Meerbeeck
Thoracic Oncology, Antwerp University Hospital, Edegem/Belgium

The significant improvement in outcome observed in immune checkpoint

SC06.04 NOVEL THERAPIES IN MALIGNANT PLEURAL MESOTHELIOMA AND THYMIC MALIGNANCIES
MONDAY, DECEMBER 5, 2016 - 14:30-15:45
Dendritic cells (DC), obtained by leukapheresis, can be loaded with synthetic material of the patient itself (autologous dendritic cell-therapy) or with other mutagenic load and the formation of neo-epitopes. Several anti PD-(L)1 antibodies are registered and/or in development for use in other tumour entities. PD-L1 is thought to induce immune tolerance. In MPM, PD-L1 expression by immunohistochemistry was reported in 20-70% of formalin-fixed paraffin embedded mesothelioma, in 70% of thymic carcinomas and in 23% of thymomas [1,3]. In mesothelioma, PD-L1 expression overexpression is more common in non-epitheloid histology, is associated with a significantly worse survival. PD-L1 expression is furthermore considered a predictive factor for the activity of immune checkpoint inhibitors in NSCLC, besides mutagenic load and the formation of neo-epitopes. Several anti PD-L1 antibodies are registered and/or in development for use in other tumour types. Promising phase 2 trial results in mostly pretreated mesothelioma patients are summarized in the table [4-6]. Expression level of PD-L1 did not correlate with response in either trial.

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There is a growing evidence of direct contributions of nicotine to cancer onset and growth. The list of cancers reportedly connected to nicotine is expanding and presently includes small-cell and non-small-cell lung cancers, as well as head and neck, gastric, pancreatic, gallbladder, liver, colon, breast, cervical, urinary bladder and kidney cancers. The mutagenic and tumour-promoting activities of nicotine may result from its ability to damage the genome, disrupt cellular metabolic processes, and facilitate growth and spreading of transformed cells. The nicotinic acetylcholine receptors (nACHRs), which are activated by nicotine, can activate several signaling pathways that can have tumorigenic effects, and these receptors might be able to be targeted for cancer therapy or prevention. There is also growing evidence that the unique genetic makeup of an individual, such as polymorphisms in genes encoding nACHR subunits, might influence the susceptibility of that individual to the pathobiological effects of nicotine. The emerging knowledge about the carcinogenic mechanisms of nicotine action should be considered during the evaluation of regulations on nicotine product manufacturing, distribution and marketing.

**SESSION SC07: NEW CHALLENGES FOR LUNG CANCER: WATERPIPES AND E-CIGARETTES**

Monday, December 5, 2016 - 16:00-17:30

**SC07.03 CONNECTIONS OF NICOTINE TO CANCER AND ITS INFLUENCE ON CANCER TREATMENT**

Sergei Grando
University of California, Irvine/CA/United States of America

There is a growing evidence of direct contributions of nicotine to cancer onset and growth. The list of cancers reportedly connected to nicotine is expanding and presently includes small-cell and non-small-cell lung cancers, as well as head and neck, gastric, pancreatic, gallbladder, liver, colon, breast, cervical, urinary bladder and kidney cancers. The mutagenic and tumour-promoting activities of nicotine may result from its ability to damage the genome, disrupt cellular metabolic processes, and facilitate growth and spreading of transformed cells. The nicotinic acetylcholine receptors (nACHRs), which are activated by nicotine, can activate several signaling pathways that can have tumorigenic effects, and these receptors might be able to be targeted for cancer therapy or prevention. There is also growing evidence that the unique genetic makeup of an individual, such as polymorphisms in genes encoding nACHR subunits, might influence the susceptibility of that individual to the pathobiological effects of nicotine. The emerging knowledge about the carcinogenic mechanisms of nicotine action should be considered during the evaluation of regulations on nicotine product manufacturing, distribution and marketing.

**Keywords:** Cancer, Nicotinic acetylcholine receptor, nicotine
SC08.01 IMPACT AND MANAGEMENT OF CO-MORBIDITIES
Alessandro Brunelli
St. James’ University Hospital, Leeds/United Kingdom

Introduction: Due to general ageing population, many patients with lung cancer are elderly and with frequent underlying co-morbidities. The most frequent co-morbidities associated with lung cancer are cardiac (i.e. coronary artery disease) and pulmonary diseases (i.e. COPD). Cardiac co-morbidity: Coronary artery disease (CAD) is present in up to 10-15% of lung resection candidates. The risk of major adverse cardiac events (MACE) and cardiac mortality is 4-fold higher in patients with previous history of CAD1 and patients with a previous coronary stent procedure within 1 year from lung resection. Invasive ventilation is associated with a mortality rate of 3.9% and an admission rate to surgical ward, respectively2. Cardiac evaluation is therefore particularly important in this population to optimize their treatment and reduce surgical risk. A specific cardiac risk score was recently developed and is named Thoracic CRCI (THRCRI). Patients in the highest class of risk had a incidence of MACE of 23% versus only 1.5% in those in the lowest class of risk. THRCRI findings were subsequently validated by a number of independent studies. Detailed evaluation for coronary heart disease is not recommended in patients who have an acceptable exercise tolerance and with low cardiac risk score. For patients whose exercise capacity is limited, those with a THRCRI >1.5 or those with known or newly suspected cardiac condition, non-invasive cardiac evaluation is recommended as per AHA/ACC guidelines to identify patients needing more invasive interventions. Appropriately aggressive cardiac interventions should be instituted prior to surgery only in patients who would need them irrespective of the planned surgery. However, prophylactic coronary revascularization in patients who otherwise do not need such a procedure does not appear to reduce perioperative risks. Pulmonary co-morbidity: Approximately 20-25% of patients with early stage lung cancer have a concomitant moderate to severe COPD (FEV1<80% and FEV1/FVC ratio <-70%). Many studies have shown the association between FEV1 and risk of postoperative lung resection (ppoFEV1 and surgical risk). In particular the risk of pulmonary morbidity and mortality has been shown to increase when FEV1 is below 50-60% or ppoFEV1 <30-40%. However, recent evidence has shown that even patients with moderate to severe COPD and lung cancer can undergo safely to lung resection. In these patients, the resection usually produces a bronchoconstriction containing the tumor and determine a minimal lost or even an improvement in respiratory mechanics and elastic recoil, similar to what happens in typical end-stage emphysema patients candidates to lung volume reduction surgery. Nearly one third of COPD patients may improve their FEV1 after lung resection. It is therefore necessary to estimate the risk of pulmonary morbidity and mortality for patients with a moderate to severe COPD. In this scenario, the FEV1 or ppoFEV1 is associated with increased morbidity and mortality, most recent guidelines recommended against using this parameter alone to exclude patients from surgery even in case of very low values5,6. Patients with idiopathic pulmonary fibrosis (IPF) and lung cancer are a more challenging population to manage. Surgical treatment of these patients is high risk for postoperative acute exacerbations of IPF, which is associated with 80-100% mortality rate. The postoperative mortality rate of these patients has been reported to range between 7 and 18%. Moreover, long-term prognosis of IPF itself affects long term survival after lung surgery for cancer. The Lung Fibrosis Risk Index (LFR) is the rationale behind the most recent recommendations to measure DLCO systematically in all lung resection candidates. Cardiopulmonary exercise test: Measurement of monoxide lung diffusion capacity (DLCO) appears to be a more sensitive indicator of poor pulmonary function and more reliably associated with postoperative respiratory complications and mortality. Until recently, DLCO measurement has been mainly reserved to patients with abnormal FEV1. However, it has been shown that DLCO and ppoDLCO are poorly correlated and that more than 40% of patients with normal FEV1 (>80%) may have reduced DLCO. A low DLCO or ppoDLCO is a reliable predictor of cardiopulmonary morbidity and mortality not only in patients with COPD but also in those with normal respiratory function. This is the rationale behind the most recent recommendations to measure DLCO systematically in all lung resection candidates. Additional fitness tests: Measurement of monoxide lung diffusion capacity (DLCO) appears to be a more sensitive indicator of poor pulmonary function and more reliably associated with postoperative respiratory complications and mortality. Additional fitness tests: Cardiopulmonary exercise test: Cardiopulmonary exercise test is the gold standard in preoperative evaluation of lung resection candidates. In addition to the most frequently used parameter, VO2max, it provides several other direct and derived measures that permit, in case of a reduced exercise capacity, to precisely identify possible deficits in the oxygen transport system. Several series have shown that a VO2max greater than 35 is associated with increased respiratory complications and mortality after lung resection. We found that the mortality rate of patients with VO2max<35 was 7% versus only 0.6% of those with lower values. The association between this parameter and respiratory complications remained the same for patients with and without COPD and for those with VO2max of greater or lower than 15 mL/kg/min. VATS and sublobar resections: Videoassisted thoracoscopic surgery (VATS) has been recommended as the approach of choice for stage I lung cancer patients. Several studies showed that this approach is associated with lower incidence of complications, shorter hospital stay and in some cases lower mortality rates compared to thoracotomy for the benefit of VATS in patients who are considered poor candidate for surgical treatment due to preexisting co-morbidities and lower pulmonary function. Large series found that the difference in pulmonary complication rates after lobectomy by VATS versus thoracotomy was present only in patients with a FEV1<60%. But coll.8 found that patients with ppoFEV1<40% or ppoDLCO<40% and submitted to VATS lobectomy had a markedly reduced incidence of these complications compared to those operated on through thoracotomy (ppoFEV1<40%: 0.7% vs. 4.8%, p=0.003; ppoDLCO<40%: 2% vs. 5.2%, p=0.003). Recent evidences have shown that anatomic segmentectomies provide equivalent oncologic results compared to lobectomy for tumours smaller than 2 cm, whilst preserving much more lung and being associated with lower incidence of postoperative complications9,10. This extent of resection appears therefore ideal for patients with a limited baseline pulmonary function. Selected References: 1. Brunelli A, et al. Recalibration of the revised cardiac risk index in lung resection candidates. Ann Thorac Surg. 2010;90(1):199-203. 2. Fernandez FG, et al. Incremental risk of prior coronary arterial stents for pulmonary resection. Ann Thorac Surg. 2013 Apr;95(4):1212-8. 3. Fleisher LA, et al. 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SC08.04 SABR VERSUS SURGERY
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In recent years, the number of early stage lung cancers has enormously increased and this tendency is more prominent in octogenarians. Both curability and non-invasiveness should be required for such situation. Surgery is the standard treatment for early stage lung cancer and VATS lobectomy or sublobar resection have been routinely recommended for patients to maintain performance status8. Especially, the indication of sublobar resection is considered to be related to the aggressive nature of tumors, thus several studies by HRCT findings and PET-CT were performed to predict the invasive nature as well as clinical stage. In JCOG 2001, kagawa et al. who received lobectomy and mediastinal lymph node dissection due to stage I NSCLC were enrolled prospectively. Pathological non-invasive cancer (both vascular and lymphatic invasion negative) was evaluated by the combination/tumor ratio on preoperative HRCT. Adenocarcinoma <2.0 cm with <0.25 consolidation to the maximum tumor diameter (35 patients, 12%) revealed pathological non-invasiveness in 98.7% (95% CI 93.2-100.0%), and this criterion could be used for radiological early lung cancer11. The prognostic study of cases enrolled in JCOG2001 revealed that 5 year OS and RFS survivals of the entire patients were 90.6% and 84.7%, respectively. The 5-year OS of radiologic early and invasive adenocarcinomas were 97.1% and 92.4%, respectively (p=0.259). If the combination/tumor ratio lower than 0.5 in cT1b-a was used as a cutoff, the 5-year OS of radiologic early (121 patients, 22.2%) was 96.7% and invasive adenocarcinomas, 88.9% (p=0.011). Based on the criteria of radiologic early cancer obtained by JCOG2001, randomised

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SC09.02 THE QUEST FOR HIGH QUALITY AFFORDABLE RADIOTHERAPY IN DEVELOPING COUNTRIES
Osama Mohamad, Hak Choy

In 2030, 60% of all new cancer diagnoses (15/25 million cases) and 80% of cancer related deaths (10/13 million deaths) will occur in low and middle income countries (LMICs). 1

Phase 3 trial to evaluate non-inferiority in OS of segmentectomy compared to lobectomy (JCOG0802). The maxSUV of the primary tumor on PET/CT could be used as a prognostic marker of early stage lung cancer. Analyses of 610 resected stage IA adenocarcinoma showed that maxSUV and GGO ratio cutoffs to predict recurrence were 2.9 and 25%, respectively. They were also related to nodal metastasis, histological tumor invasiveness and recurrence. The 5-year RFS of cases with maxSUV<2.9 (n=456) was 95%, while cases with maxSUV>2.9 (n=154), 72% (p<0.001). 2 Surgical management of early stage lung cancer should be selected by both PET/CT and maxSUV to predict the biological malignancy of each case. Stereotactic ablative radiotherapy (SABR) has attained importance for efficacy and safety for the treatment of early cancers located in the peripheral lung. There are two representative randomised phase 3 trial (STARS and ROSEL) to compare SABR and resection. Eligible patients of these studies were T1-2a (<4cm) N0M0 and a total of 58 cases were registered (31 received SABR and 27, surgery). The combined analysis of these two studies revealed that 3 year OS in SABR (95%) was superior to that of surgery (79%) (p<0.037) and RFS at 3 years was 74% in SABR versus 64% in surgery (p<0.04). Only 10% of cases in SABR group suffered grade 3 toxicity but 44% of surgery group developed grade 3 and 4 toxicities. The pooled analysis of the two studies showed SBRT had similar treatment efficacy to that of surgery in spite of the small sample size. 3 Japan Clinical Oncology Group evaluated the efficacy and safety of SBRT for operable/inoperable T1N0M0 patients (JCOG D403). A total of 164 patients (88 stage IIA non-small cell lung cancer: A pooled study of 46 Gy. The 3 year OS was 59.9% in inoperable patients and 75.6% in operable patients. 4 Investigations into the effectiveness of SABR for operable patients as well as the optimal indication, dose fraction and schedule be clarified by respective prospective monocentric randomized trials. SABR has become a radical treatment for inoperable stage I lung cancer. In addition, if operable cases treated by SABR in JCOG0403 show favorable outcome, further comparable trial of SABR versus less invasive surgery should be warranted. References 1) Committee for Scientific Affairs The Japanese Association for Thoracic Surgery, Thoracic and cardiovascular surgery in Japan in 2013: Annual report by the Japanese Association for Thoracic Surgery. Gen Thorac Cardiovasc Surg.2015;63:670-701. 2) Suzuki K, Koike T, Akasawa T, et al. A prospective radiological study of thin-section computed tomography to predict pathological noninvasiveness in peripheral clinical IA lung cancer (Japan Clinical Oncology Group 2001). J Thorac Oncol 2011;6:761-756). 3 Asamura H, Hishida T, Suzuki K, et al. Radiographically determined noninvasive adenocarcinoma of the lung: Survival outcomes of Japan Clinical Oncology Group 2001) Thorac Cardiovasc Surg 2013;146:24-30. 4) Nakamura K, Saji H, Nakajima R, et al. A Phase III Randomized Trial of Lobectomy Versus Limited Resection for Small-sized Peripheral Non-small Cell Lung Cancer. J Thorac Oncol 2012;7:212-20. 5) Uehara H, Tsuchiya K, Okumura S, et al. Prognostic Role of Positron Emission Tomography High-Resolution Computed Tomography in Clinical Stage IA Lung Adenocarcinoma Ann Thorac Surg 2013;96:1958–1965 6) Chang JY, Tomography and High-Resolution Computed Tomography in Clinical Stage IA Lung Adenocarcinoma Ann Thorac Surg 2013;96:1958–1965 6) Chang JY, Tomography and High-Resolution Computed Tomography in Clinical Stage IA Lung Adenocarcinoma Ann Thorac Surg 2013;96:1958–1965 6) Chang JY, Tomography and High-Resolution Computed Tomography in Clinical Stage IA Lung Adenocarcinoma Ann Thorac Surg 2013;96:1958–1965 6) Chang JY, Tomography and High-Resolution Computed Tomography in Clinical Stage IA Lung Adenocarcinoma Ann Thorac Surg 2013;96:1958–1965

Keywords: early lung cancer, segmentectomy, SABR

SESSION SC09: RADIOTHERAPY FOR A GLOBAL CANCER MONDAY, DECEMBER 5, 2016 · 16:00-17:30

SC09.02 THE QUEST FOR HIGH QUALITY AFFORDABLE RADIOTHERAPY IN DEVELOPING COUNTRIES
Osama Mohamad, Hak Choy

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In 2030, 60% of all new cancer diagnoses (15/25 million cases) and 80% of cancer related deaths (10/13 million deaths) will occur in low and middle income countries (LMICs). 1 This explosive growth is attributed to prolonged life expectancy in steadily growing populations with high levels of modifiable risk factors such as tobacco/alcohol and unhealthy diets. Despite the significant health burden, LMICs spend less than 10% of the global cancer budget. Cancer therapies are exponentially sprouting in high income countries but LMICs are not proportionally benefiting from this growth. Corruption, lack of infrastructure, poverty, and absence of national cancer policies/goals have hindered the development of quality cancer care programs. Radiotherapy has particularly suffered because of the perceived assumption that establishing quality radiotherapy centers in LMICs is unaffordable, non-sustainable and therefore unattainable and should not be pursued. Currently, up to 90% of LMIC inhabitants lack sufficient radiotherapy access and about 30 countries in Africa do not have a single treatment machine. It is estimated that by 2020, ~9000 treatment machines, ~70000 radiotherapy oncologists, and thousands of physicists and therapists are needed to treat patients in LMICs per evidence-based radiotherapy recommendations [2]. Recently, a group of experts with the Lancet Oncology Commission [3] reviewed the current radiotherapy capacity in LMICs and estimated the 20-year burden of cancer requiring radiotherapy and the needed investments to reach the optimal capacity size. External funding and radiotherapy equipment is needed to the needed levels. The published report provides compelling evidence that investment in radiotherapy not only will save millions of lives but will also bring significant economic benefits. The initial capital costs of scaling up radiotherapy may appear prohibitive, but these figures are based on conservative projections and project that promise to deliver radiotherapy that is safe, timely, effective, efficient, equitable and patient centered. By aiming at quality care delivery, we can guarantee the highest returns on investments not only in oncologic outcomes but also in curbing loss in health-related productivity and life years. We hereby discuss few strategies to directly or indirectly reduce the capital and operating costs of such an expansion - Trans national, public and private partnerships: International organizations such as the WHO, IAEA, etc in collaboration with interested academic consultants and national governments should plan the required radiotherapy centers based on individualized national cancer priorities in the setting of a wide cancer care policy. TH 44 The governments which are expected to establish effective social security systems with universal health coverage, create reliable cancer registries, implement effective cancer preventative and early diagnosis programs and finally promote oncologists, and thousands of oncologists and therapists. Once international investments are coupled to national needs/efforts, minimal wasting of resources and maximal return on investment will be attained.

Centralization and pooling of resources regionally and internationally. This is a crucial step to at least jump start radiotherapy programs especially in the very low income countries. Features of international centers can create circles of remote dosimetry physicists and chart rounds via video conferencing to promote continued education and high quality treatment plans. These regional networks can be also connected to international cancer centers of excellence for further support and collaboration. Tox breaks can be offered to academic institutions or manufacturers in countries can participate in this process. Investing in technology/science. The development departments should be offered incentives to create these tools. Optimizing the use of radiotherapy techniques a major strategy to optimize radiotherapy utilization and decrease operating cost ratio. Hypofractionation: The number of “radiation fractions per year” is used as a surrogate for radiotherapy demand. Hypofractionation, thus, is a major strategy to optimize radiotherapy utilization by decreasing operating costs without compromising outcomes in many cancer sites. For example, in the case of 1000 early breast (4) and 1000 early prostate cancer patients requiring radiotherapy per year, using evidence-based hypofractionated treatments, not necessarily the extremely hypofractionated high-tech stereotactic radiation, would be far more cost-effective and affordable. Once the radiotherapy machines from 10 to 6 and the number of therapists from 25 to 10. It will also decrease the duration of treatment per patient and thus allow more patients to be treated daily. Despite these benefits, hypofractionation remains widely under utilized even in developed countries [6].

Table 1. Radiotherapy resources for conventional fractionation vs. moderate hypofractionation in a hypothetical population of breast and prostate cancer patients.

<table>
<thead>
<tr>
<th>Conventional Fractionation</th>
<th>Hypofractionation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast Cancer</td>
<td>Prostate Cancer</td>
</tr>
<tr>
<td># of patients/yr</td>
<td>1000</td>
</tr>
<tr>
<td>Fraccion per treatment</td>
<td>32</td>
</tr>
<tr>
<td>Total # of fractions</td>
<td>25,000</td>
</tr>
<tr>
<td>Required # of therapists</td>
<td>10</td>
</tr>
<tr>
<td>Required # of machines</td>
<td>100</td>
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</tbody>
</table>

*Based on 250 works per day; Based on 25 patients per machine per day.

Investing in building local skills: Skilled radiation oncologists, therapists and physicists are very expensive commodities. While initial external support is crucial, new radiation centers need to eventually become self-sufficient and sustainable. Establishing local manufacturing programs in developing countries to decrease the cost of external training and limit brain drain. There is no magic wand to decrease the initial cost of investing in building radiotherapy capabilities but through careful planning and strong collaborations, millions of lives can be saved. Cost is crucial but we should not
lose compass of our goal: delivering quality radiotherapy treatments to cure, improve the quality of life and alleviate pain in of millions of patients with cancer who are desperately in need.

Keywords: affordability radiotherapy LMIC developing

**SC09. RADIOThERAPY FOR A GLOBAL CANCER**

**MONDAY, DECEMBER 5, 2016 - 16:00-17:30**

**SC09.04 RADIOThERAPY IN CHINA**

Luhua Wang, Jiade Lu, Jinyi Lang

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Cancer incidence and mortality have been increasing in mainland China, making cancer the leading cause of death since 2010 and a major public health problem in the country. Much of the rising burden is attributable to population growth and ageing and to socio-demographic changes. According to the National Central Cancer Registry of China (NCCR), an estimated 4,292,000 new cancer cases and 2,814,000 cancer deaths would occur in mainland China in 2015, with lung, stomach, esophagus, liver and colorectal cancer being the five most common incident cancers and the leading cause of cancer death, for which radiotherapy usually plays an important role in the comprehensive therapy. The earliest record of radiation therapy for cancer in China dates back to the early 1930s. The establishment of the Sino-Belgian Radium Institute in 1931 signified the initiation of modern radiation oncology in China. However, the development of cancer treatment has been hampered by several major wars and political turmoil in the following decades until the late 1970s and early 1980s: the era of national economical reform in mainland China. It was at this point when the academic and research bodies started to focus on the availability of radiation oncology service and their access by cancer patients. In the next 30 years, China has undergone a period of incredible economic growth and radiotherapy has clearly improved in terms of equipment and its utilization, although the shortage of facilities and workforce remain to be improved. The Chinese Society of Radiation Oncology (CSTRO) started its survey of the personnel and equipment in radiation oncology in mainland China since 1986. The updated survey results of 2015 were recently compiled and analyzed. Comparison of these crucial data clearly demonstrates the increase in the number of the facilities as well as advances in the quality of service (Figures 1 and 2). Based on the report of the third survey (of 1997) (first English-vision survey published in the International Journal of Radiation Oncology * Biology * Physics), there were 453 radiation oncology centers equipped with 286 linear accelerators, 381 cobalt units, 179 deep X-ray machines, and 302 brachytherapy units. These facilities were staffed with 3,440 physicians, 423 physicists, and 2,245 radiation therapists. It is important to note that less than 1,200 physicians were trained at major cancer centers within the radiation oncology specialty. The rest were of other specialties (e.g., surgeons) and received only several months of “practical training” (i.e., mentorship by experienced radiation oncologist with customized lectures) in a few major cancer centers mostly in major cities such as Beijing, Shanghai, and Guangzhou, rather than formal residency training in radiation oncology. The ratio of medical physicists to radiation oncology centers was less than 1:1 as well. (Figure 1) The two decades after 1997 signifies a rapid advance in the quality of radiation therapy facilities as well. The number of linear accelerators exhibited a nearly 6-fold increase in these 20 years, and more facilities are now equipped with computerized treatment planning systems (increased from 177 to 1,921) as well. On the other hand, the registered radiation oncology centers were established in most of the major cities, increased to 1,431 (a 210% increase from the 1997 survey), which makes radiotherapy much more easily accessed by cancer patients. The number of radiation oncologists increased to 5,851 (a 360% increase). Besides, medical physicists, a crucial specialty for the quality and safety of the clinical application of radiotherapy, has substantially improved. The number of trained medical physicists has undergone a nearly 7-fold increase to 3,294 in total. (Figure 2) At the same time period for accelerated development regarding radiation therapy capacity, the population and cancer incidence of mainland China had also increased, which resulted in the radiotherapy remained much insufficient. According to the recent cancer statistics in mainland China, the cancer incidence was 4.29 million in 2015. Given that approximately 50% require RT as part of definitive treatment, around 2.15 million Chinese cancer patients need RT annually. This number is most likely higher, since it does not include recurrent and palliative indications (estimates put this number into the 65-75% range for all malignancies), and cover all the area in mainland China. In fact, the numbers of annual new radiotherapy consultation and daily treatment was 919,339 and 76,612, respectively. Therefore, only 50% patients who would need radiotherapy received radiotherapy in Mainland China in 2015. The current status is caused by two main reasons. First, the ratio of tele-therapy facility (linear accelerator and Co60 combined) per million was 1.49 in 2015, which are quite low compared to 8.2 in the United States, 7.5 in France, 3.4 in the United Kingdom, and 2-3 recommended by the World Health Organization. Second, the distribution of radiotherapeutic resources is uneven by region.

For example, the ratio in Beijing, Tianjin, Shanghai, and Shandong municipalities/province, where are considered regions of better economic development, is 3.07, 3.28, 2.15, and 2.28, respectively. Meanwhile, rural and/or less populous regions such as Tibet are often under 1.00. In conclusion, it is still obvious that cancer patients have limited access to radiotherapy facilities as well as qualified radiation oncologist, though remarkably robust development in all facets of radiation oncology over the last 30 years in mainland China. Clearly, much more effort should be made in regards to access to radiation oncology facilities and their service for cancer patients.

**Figure 1.** The growth radiation therapy equipment in China from 1986 to 2015 based on the 2015 CSTRO report by Lang et al.

**Figure 2.** The changes in the configuration of radiotherapy team in China from 1986 to 2015 based on the 2015 CSTRO report by Lang et al.

Keywords: radiation therapy, equipment, Mainland China

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**SESSION SC10: SQUAMOUS CELL NSCLC**

**MONDAY, DECEMBER 5, 2016 - 16:00-17:30**

**SC10.03 ANTI-EGFR MONOCLONAL ANTIBODIES IN SQUAMOUS CELL NSCLC**

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Keywords: radiation therapy, equipment, Mainland China
Patients with advanced squamous NSCLC receive first-line chemotherapy with a platin-based doublet. Combining first-line chemotherapy with EGFR-directed monoclonal antibodies has been studied as a strategy to improve outcomes in these patients. Anti-EGFR monoclonal antibodies inhibit EGFR-mediated signal transduction and may also act via immunological mechanisms. Several monoclonal antibodies have been studied within clinical trials and data from phase III trials are available for cetuximab and necitumumab (for review see ref. 1). Two randomized phase III trials compared chemotherapy plus cetuximab with chemotherapy alone in patients with advanced NSCLC (2, 3). The FLEX trial demonstrated improved overall survival for cetuximab added to chemotherapy in patients with advanced NSCLC and enriched for EGFR expression in their tumors (2). The hazard ratio was 0.87 (p=0.044), median survival times were 11.3 months and 10.1 months, and 1-year survival rates were 42% and 32%, respectively. For patients with high EGFR expression (n=347), the hazard ratio was 0.80 and median survival times were 10.2 months and 8.9 months, respectively. The BMS 099 trial failed to show an improvement in progression-free survival for cetuximab added to carboplatin plus paclitaxel in unselected patients with advanced NSCLC (3). A meta-analysis based on individual patient data from four randomized trials demonstrated a survival benefit for chemotherapy plus cetuximab compared to chemotherapy alone (4). The hazard ratio was 0.88 (95% CI 0.79-0.97; p=0.009). The benefit was greater in patients with squamous NSCLC in whom a hazard ratio of 0.77 (95% CI 0.64-0.93) was seen. Necitumumab has been studied in two phase III trials (5, 6). The SQUIRE trial assessed cisplatin plus gemcitabine with or without necitumumab in 1,093 patients with advanced squamous NSCLC (5). Necitumumab was intravenously administered at a dose of 800 mg in days 1, 8, and 15 every 21 days and was planned to be continued until the end of chemotherapy until disease progression or intolerable toxicity. Necitumumab improved the outcome of chemotherapy. The hazard ratio was 0.84 (95% CI 0.74-0.96; p=0.012). Median survival times were 11.5 months and 9.9 months, and 1-year survival rates were 47% and 42% for the chemotherapy plus necitumumab arm and chemotherapy arm, respectively. Progression-free survival and response rates were also improved with the combined treatment. Grade ≥3 adverse events more frequently seen with chemotherapy plus necitumumab compared to chemotherapy were skin rash and hypomagnesemia. Based on these results, necitumumab has been approved as a first-line therapy of squamous NSCLC in combination with cisplatin and gemcitabine. In contrast to the SQUIRE trial, the INSPIRE trial was prematurely stopped after enrolment of 634 patients because an interim analysis showed increased thrombo-embolic events and a lack of benefit for the combined treatment (6). Research has also focussed on the characterization of predictive biomarkers. Immunohistochemical EGFR protein expression and EGFR FISH positivity were of particular interest. In the FLEX trial, immunohistochemical EGFR expression of tumor cells was prospectively assessed by means of the DAKO pharmDx kit (7). Membrane staining intensity was divided into no staining, weak staining (1+), and strong staining (2+). The fractions of cells at the various staining intensities were determined. An immunohistochemistry score (IHC) based on both intensity and frequency of staining was then used for further analysis on the association between EGFR expression levels and chemotherapy benefit. Patients were divided those with high (IHC score ≥200) and those with low IHC score (<200) EGFR expression. High EGFR expression was seen in 31% of the patients. Among patients with high EGFR expression, patients treated with chemotherapy plus cetuximab had prolonged survival compared to those treated with chemotherapy alone. The hazard ratio was 0.74 (95% CI 0.56-0.99; p=0.031), median survival times were 12.2 months, and 1-year survival rates were 50% versus 37%. Among patients with low EGFR expression, survival times were not different between the two treatment arms. The treatment interaction between EGFR expression levels and treatment effect was statistically significant (p=0.04). The survival benefit achieved by the addition of cetuximab to chemotherapy in patients with high EGFR expression was seen across most subgroups including all major histological subgroups. Among patients with squamous NSCLC and high EGFR expression, the hazard ratio was 0.62 (0.43-0.88) in favour of cetuximab plus chemotherapy compared to chemotherapy alone. The survival benefit by the addition of cetuximab to chemotherapy in patients with squamous NSCLC was achieved without an increase in toxicity. In summary, patient selection based on EGFR expression levels resulted in a clinically meaningful improvement in the risk benefit assessment of platinum-based first-line chemotherapy plus cetuximab in patients with advanced NSCLC (2). The SWOG-S1010 study indicated that high EGFR positivity predicted benefit from cetuximab, particularly in patients with squamous NSCLC (8). Similarly, the benefits from necitumumab appeared to be greater in patients with EGFR FISH positivity or high EGFR expression (9, 10). References: 1. Pierer R, et al. Lancet Oncol 2015, 27, 874-885. 2. Pierer R, et al. Lancet 2009, 373, 1525-31. Lynch Tj et al. Clin Oncol 2010, 28, 911-7. 3. 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SESSION SC11: ALK, ROS1 AND RARE MUTATIONS IN NSCLC
MONDAY, DECEMBER 5, 2016 - 16:00-17:30

SC11.03 ROS1 AS A THERAPEUTIC TARGET IN ADVANCED NSCLC
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In non-small cell lung cancer (NSCLC) chromosomal rearrangements involving the receptor tyrosine kinase ROS1 have been first described in 2007 (1). These aberrations have been shown to trigger constitutive kinase activity and activation of downstream pathways like the MAPK pathway. ROS1 rearrangements can be found in about 2% of lung adenocarcinoma and are associated with female gender and never-smoking status (2). Different fusion partners have been described. In routine diagnostic ROS1 fusion genes can be reliably detected by fluorescence in situ hybridization (FISH; e.g. dual color break apart FISH), RT-PCR or next-generation sequencing (NGS). ROS1 fusions occur mutually exclusive of aberrations in EGFR, ALK and KRAS. However, using NGS, co-occurring mutations, preferentially in TP53, but also in other genes involved in oncogenic pathways, can be found in about 50% of these patients (3). ROS1 fusions also seem to be of prognostic relevance, since remarkable long survival times have been described in patients treated with chemotherapy only (3). The FDA granted crizotinib (Molecular Targets) inhibitor approval in August 2015 for a US trial cohort of 50 ROS1 positive patients with advanced, mostly pretreated lung adenocarcinoma and showed impressive activity (6). The overall response rate (ORR) was 72% (95% CI 51 to 84) with 3 complete responses. Median progression free survival (PFS) was 19.2 months (95% CI 14.4 to not reached). Treatment was well tolerated and the side effect profile resembled that observed in the treatment of ALK positive lung cancer with crizotinib. A similar ORR of 80% was reported in a retrospectively analyzed European cohort (5). However, PFS was only 9.1 months in these patients. The EUCROSS trial, a collaborative study of the German Lung Cancer Group Cologne and the Spanish Lung Cancer Group, is a prospective European phase II trial which recruited 34 ROS1 positive patients between June 2016 and September 2015. ROS1 fusion genes were diagnosed using dual color break apart FISH and the results were confirmed by next-generation sequencing. With an ORR of 69% (95% CI, 43.1 to 84.3) similar efficacy has been reported (6). Based on its high activity and favorable toxicity profile, crizotinib is now approved for the treatment of ROS1-positive NSCLC by the FDA since March 2016 and by the EMA since August 2016. Treatment of ROS1-positive NSCLC with crizotinib thus has become standard first-line treatment in the leading international guidelines. Current challenges for the further development and improvement of targeted treatment of ROS1-positive patients are (I) implementation of ROS1 diagnostics in routine molecular diagnostics and (II) development of next-generation ROS1 inhibitors overcoming crizotinib resistance. The increasing number of actionable mutations in NSCLC including ROS1 requires implementation of molecular testing, since validated single gene assays are no more feasible given the usually limited biopsy tissue specimens. However, conventional NGS technology is restricted to point mutations and does not cover copy number variations (CNV) and gene fusions. Thus, new NGS technologies have to be integrated in routine diagnostics like highly sensitive capture-based NGS, which does not require DNA PCR and thus allows to detect reliably CNV and gene fusions. While increasing knowledge of the molecular mechanisms underlying TKI resistance has led to the development of a series of highly potent next-generation inhibitors in ALK-positive NSCLC now, resistance of ROS1-positive patients to crizotinib is incompletely understood. In preclinical studies as well as in biopsy tissue, somatic mutations in the ROS1 kinase domain associated with acquired crizotinib resistance have been described (7). In functional studies these mutations were associated with different degrees of resistance. Alternatively, bypass activation of oncoprotein signaling pathway has been described as mechanism underling resistance. For instance, an activating mutation and EGFR pathway activation have been reported in single cases (8). In vitro, the multikinase inhibitors cabozantinib, foretinib and lorlatinib have been shown to overcome crizotinib resistance triggered by secondary mutations in ROS1. Response in humans has also been reported in a ROS1-positive patient with a mutation conferring resistance to crizotinib (10) and was also observed in a phase I trial of lorlatinib in the same clinical setting. In summary, ROS1 positivity characterizes a subgroup of patients with a major benefit from treatment with crizotinib. Consequently, crizotinib has become the current standard of care for these patients. However, resistance should be available before decision on first-line treatment. Acquired resistance to crizotinib may be caused by mutations in the ROS1 kinase domain or by activation of bypass pathways. The multikinase inhibitor cabozantinib and the next-generation ALK/ROS1 inhibitor lorlatinib have shown promising efficacy in early clinical evaluation. Rikova K et al. Global survey of phosphoryrosine signaling identifies oncogenic kinases in lung cancer. Cell 2017, 14; 131(6):1190-203. (2) Bergethon K et al. ROS1 rearrangements define a unique molecular class of lung cancers. J Clin Oncol 2015, 33(8):867-76. (3) Michels E et al. EUROCROS: a prospective European phase II trial to evaluate efficacy and safety of crizotinib in advanced adenocarcinoma of the lung harboring ROS1 translocations. WCLC 2016 (oral presentation). (7) Awas MM et al. Acquired resistance to crizotinib from a mutation in CDFA-ROS1. NEJM 2013, 369(1):337-40. (8) Arazumaa MM et al. Activity of PDGFRA TKIs for PDGFR-α mutations in ROS1-positive lung cancer. J Thorac Oncol 2016, 11(8):1273-81. (9) Davies KD et al. Resistance to ROS1 inhibition mediated by EGFR pathway activation in non-small cell lung cancer. PLoS One 2013, 13(8):e22395. (10) Drilon A et al. Novel crizotinib-resistant solvent-front mutation responsive to cabozantinib therapy in a patient with ROS1-rearranged lung cancer. Clin Cancer Res 2016, 22(10):2351-8.

References
SESSION SC13: INTERACTION OF COPD AND LUNG CANCER – CONSEQUENCES FOR EARLY DIAGNOSIS AND MANAGEMENT
TUESDAY, DECEMBER 6, 2016 - 11:00-12:30

SC13.02 INCREASED RISK FOR LUNG CANCER IN COPD
Stephen Lam

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Globally, chronic obstructive pulmonary disease (COPD) and lung cancer are among the top 5 causes of death. The two diseases share common risk factors such as tobacco smoking, outdoor and household air pollution. COPD is associated with a two to four fold increased risk for lung cancer independent of smoking. COPD can be characterized by symptoms, lung function criteria (forced expiratory volume in one second (FEV<sub>1</sub>) < 80% predicted for age, gender and height, FEV<sub>1</sub>/forced vital capacity (FVC) < 0.7, or diffusing capacity < 80%). COPD has also been defined by computed tomography (CT) changes such as pulmonary emphysema by visual examination or by quantitative measurement (percent voxels < 950 HU based on a threshold of 4.8%) or air trapping from comparison between inspiratory and expiratory CT scans. In the PLCO <sup>3</sup> risk prediction model, self-reported COPD was significantly associated with lung cancer risk (OR 1.45, 95% CI: 1.25-1.67). The added value of the AUC was 0.500 and 0.503 with and without a history of COPD was 0.800 and 0.799 respectively (M. Tammegam, personal communication). A study in British Columbia examined the incremental value of pulmonary function test in 2,596 ever smokers above 40 years of age who had smoked ≥20 pack-years. One hundred and thirty-nine participants developed lung cancer after a median follow-up of 7.7 years. Lower FEV<sub>1</sub> % increased the lung cancer risk for both men and women, but did so more strongly for men than in women (interaction P<0.001). FEV<sub>1</sub> % was more strongly for men than in women (interaction P<0.001). Lower FEV<sub>1</sub>% increased the lung cancer risk for both men and women, but did so independent of smoking.

Keywords: NSCLC, Driver Mutations, Targeted Therapies

SC13.03 LIMITATION BY COPD FOR DIAGNOSTIC PROCEDURES
Gyula Ostoros<sup>1</sup>, János Varga<sup>2</sup>, Anna Kerpel-Fronius<sup>3</sup>


Limitation by COPD for Diagnostic Procedures Ostoros, Gy. Varga, J. and Kerpel-Fronius A. National “Korányi” Institute for Pulmonology Hungary, Budapest Lung cancer and COPD are smoking dependent diseases. Smoking cessation is crucial before and during the diagnostic procedures because of the consequences of smoking (e.g. sputum retention, mucociliary dysfunction and potential other more serious complications after the procedures). Severe obstructive or restrictive pulmonary disorders limit the diagnostic possibilities in patients with malignant pulmonary diseases. The screening of lung cancer with low-dose CT has become the gold standard in the past decade. The two imaging-based phenotypes of COPD can be well distinguished by this technique. CT scanning can also help to identify non-diagnosed emphysema patients and may lead to early treatment of the disease. It has been shown that non-smoker emphysema patients have a similar risk of lung cancer as smokers with emphysema. Thus, patients with emphysema may be an eligible subgroup for a more intensive lung cancer screening program. However, once a suspicious lesion is found severe COPD, it can limit the choices available for differential diagnosis seriously - CT guided lung biopsies in COPD patients carries a higher risk of hemorrhage and pneumothorax. Patients with severe COPD and respiratory failure with decreased oxygen saturation limit the indication of diagnostic bronchoscopic procedures as well. The examination of exhaled breath condensate (EBC) is a non invasive process. There are efforts to discriminate lung cancer and COPD with EBC. Lung tumours have influence on the lung function. Besides the severity of COPD, the result of the lung function test (LFT) depends on the size and position of the pulmonary tumour as well. In the case of a big central tumour or a huge amount of pleural fluid, the LFT will show rather restrictive than obstructive character. A small peripheral malignancy will not change the shape and volume of the LFT. If the tumour is in the trachea or compressed it will change the inspiratory phase of the flow-volume chart could be flat. Sometimes the lung tumours could lead a misdiagnosis of COPD. A centrally located small tumour which is not visible on the chest X-ray but compresses the trachea or any of the pulmonary vessels can cause breathlessness, fatigue and decreased oxygen saturation. A mediastinal conglomeration of lymph nodes

References

Keywords: risk assessment, screening
can cause similar symptoms. Low physical activity, obesity, smoking and comorbidities are significant negative factors for risk stratification before any pulmonary diagnostic procedure as well. Pulmonary rehabilitation can improve functional reserves if functional capacity is at borderline. Pulmonary rehabilitation has positive effect on cardiovascular function, metabolism, muscle-function and lung mechanics. As for lung function parameters, we need to focus on forced expiratory volume in one second (FEV1) and diffusion capacity (DLCO). We can follow the common agreement of European Respiratory Society for risk stratification before a diagnostic pleuropneumothorax. Based on this protocol, FEV1 and DLCO need to be >35%pred. In the case of 35%pred<FEV1 and DLCO<75%pred, we need to consider VO2/kg during a cardiopulmonary exercise test. If VO2 ≥10 ml/kg/min, the patient need a pulmonary rehabilitation program to improve functional reserves. Regarding lung function, we need to focus on lung mechanics and lung kinematics as well. Lung mechanics can be monitored by resting functional reserve capacity (FRC) and residual volume (RV). Lung kinematics can be monitored by chest expansion. Improved resting or dynamic hyperinflation and lung kinematics of the patients with chest physiotherapy and complex pulmonary rehabilitation is also suggested. As a general effect of rehabilitation, training programs can improve the cardiovascular response, oxygen uptake and the metabolism. We may also focus on physical activity, which is a general prognostics marker. Physical activity can be monitored by pedometer. Obesity can influence the complications of the surgical procedure and it has some effect on lung mechanics as well. If we have time, in case of an obese patient we may also consider improving their body composition before the invasive procedure. To sum up, comorbidities have to be considered before an invasive diagnostic procedure of lung cancer. Patients with impaired pulmonary hemodynamics, ischemic heart disease, diabetes or obesity have to be carefully evaluated.


**Keywords:** diagnosis, copd, lung cancer

### SC13.04 LIMITATIONS BY COPD FOR TREATMENT

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The most common cause of death among patients with COPD is lung cancer as well as respiratory failure, and COPD often co-exists with lung cancer with a range of 40 to 70% (1). While lung cancer survival is generally very low, survival is even lower among patients with COPD, i.e. in one study, it is reported that 26% of lung cancer patients without COPD were still alive 3 years after their diagnosis compared to 10% of lung cancer patients with COPD (2). One of the main reasons why prognoses of lung cancer patients with COPD are worse is that treatment options are limited due to affected lung function. For surgical treatment for lung cancer patients with COPD, post-operative residual lung function should be maintained within a certain level. Therefore, patients with severely reduced lung function may be rejected for surgical treatment, or at least they may not able to receive standard surgical procedures. For patients rejected for surgery because of poor lung function, radiotherapy is an alternative treatment option. However, radiotherapy itself affects lung function because of post-treatment radiation pneumonia. For drug therapy, drug-induced lung toxicities are emerging issues, especially due to the use of EGF receptor tyrosine kinase inhibitors, ALK inhibitors or immune check point inhibitors (3). In cases whose lung function is severely affected, drug-induced lung toxicities may be lethal, and special attention should be payed to such patients. Therefore, to overcome these limitations of treatment is an urgent issue in the daily practice. For surgical treatment, assessment of preoperative lung function is essential to judge its indication. Both predicted post-operative lung function and DLCO values are mainly used as parameters for the indication of surgical treatment. Therefore, optimization of these functions by medical therapy, pulmonary rehabilitation and smoking cessation may extend the opportunities of surgical treatment, resulting in better patients’ outcomes. Regarding with medical therapy, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) (4) and American Thoracic Society and the European Respiratory Society guidelines for COPD management point out the use of bronchodilators as well as inhaled corticosteroids. In addition, pulmonary rehabilitations would be recommended for pre-operative lung cancer patients with poor lung function because of its safety, although there are no data clearly showing the efficacy of pulmonary rehabilitations on patients’ outcome. For radiotherapy for lung cancer patients with COPD, newly developed devices appear to show promising outcome. Both stereotactic body radiotherapy (SBRT) and ion beam radiotherapy have such a nice radiation dose distribution that high doses of irradiation are possible with low impact to normal tissues. Some reports suggest that patients’ outcomes by these treatment modalities may be not worse or sometimes better than surgical treatment (5). In addition, smoking cessation is, of course, important issue as a pre- and post- operative management. Since lung cancer patients with COPD are increasing over all area in the world, appropriate treatment should be chosen with the utmost care and attention. In addition, it is an urgent issue to establish more effective and safe treatment modalities to these patients. References 1) Young RP, Hopkins RJ, Christma T, et al. COPD prevalence is increased in lung cancer, independent of age, sex and smoking history. Eur Respir J. 2009;34(2):380-6. 2) Kim VA, Soniano J, Visel G, Fabbri L. Recent trends in lung cancer and its association with COPD: an analysis using the UK GP Research Database, Prim Care Respir J. 2010;19(1):57-61. 3) De Sanctis A, Taillade L, Vignot S, et al. Pulmonary toxicity related to systemic treatment of nonsmall cell lung cancer. Cancer. 2011;117(14):3069-80. 4) Rabe KF, Hurst S, Anzueto A, Barnes PJ. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med. 2007;176(6):532-55. 5) Chehade S and Palma DA. Stereotactic radiotherapy for early lung cancer: Evidence-based approach and future directions. Rep Pract Oncol Radiother. 2015;20(6):403-10.

**Keywords:** bronchodilator, stereotactic body radiotherapy, Surgery, lung function

**SESSION SC14: IMMUNOTHERAPY OF NSCLC TUESDAY, DECEMBER 6, 2016 - 11:00-12:30**

### SC14.01 IMMUNOTHERAPY IN THE FIRST-LINE SETTING OF ADVANCED NSCLC

Roy Herbst

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Lung cancer remains the leading cause of cancer-related deaths worldwide. Advances in screening, surgery and treatment have helped to improve the median survival for patients with lung cancer over the past decade, however, the five-year survival rate remains less than 20%. The majority of patients are diagnosed with advanced stage disease, who are treated with platinum-based chemotherapy, followed by targeted, combination, or immunotherapies. Given the response rates seen with the use of immunotherapy in the second-line setting, it was appropriate to begin to explore if these agents could be given to patients earlier in their treatment. Immunotherapies have been found to be better tolerated than chemotherapy and have the potential for long-term survival, thus could benefit patients as first-line therapy, as some patients will never go on to receive second-line treatment. Two agents, nivolumab and pembrolizumab, both monoclonal antibodies targeting programmed cell death protein 1 (PD-1), are approved for use in patients with non-small cell lung cancer (NSCLC) who have received prior chemotherapy. The KEYNOTE-024 randomized phase III trial of pembrolizumab vs. standard of care (platinum-based chemotherapy), demonstrated superior progression-free survival (PFS) and overall survival (OS) for first-line treatment in patients with tumors expressing high levels of programmed cell death ligand 1 (PD-L1) (tumor proportion score ≥50%). The CheckMate-026 randomized, phase III study of nivolumab vs. standard of care in treatment-naive patients with tumors expressing ≥5% PD-L1 did not meet the primary endpoint of PFS. For this presentation, the use of predictive markers in the front-line setting will be discussed and implications for combination therapy will be reviewed.

**Keywords:** NSCLC, PD-L1, Immunotherapy

### SC14.04 THE CD47 MACROPHAGE CHECKPOINT AS A NEW IMMUNOTHERAPY TARGET


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3Institute for Stem
Background: Hu5F9-G4 is a humanized monoclonal antibody that targets CD47, blocking its anti-phagocytic “don’t eat me” signal through macrophage receptor SIRPs, leading to tumor phagocytosis. CD47 is overexpressed on human cancer cells and also on red blood cells (RBCs). In preclinical studies, Hu5F9-G4 caused a transient anemia that was improved with a single lower Priming Dose allowing higher Maintenance Doses. Materials and Methods: Relapsed/refractory solid tumors and lymphomas were included. The dose escalation study included: Part A, to determine the Priming Dose and Part B, to determine the Maintenance Dose. The maximum tolerated dose (MTD) in part A was used for the single Priming Dose in part B (Hu5F9-G4 0.1 mg/kg was selected as the Priming Dose, with no >2 grade 3 anemia. Pharmacodynamic studies show almost 100% RBC receptor occupancy at the Priming Dose. Treatment-related adverse event (TRAe) in Part A included: anemia (3 G1, 3 G2), hyperbilirubinemia (3 G1, 2 G2; unconjugated), headache (6 G1, 1 G2), on PHS (3 G1), and nausea (3 G1). Part B included 3 (N=4), 10 (N=3), and 20 mg/kg (N=6, ongoing). There have been no DLTs in 3 patients on 20 mg/kg, and one DLT (headache with hemagglutination) in 6 patients at the 20 mg/kg maintenance dose (ongoing). Most toxicities were associated with the initial single Priming Dose and were completely reversible. TRAE in Part B at 3 mg/kg included: anemia (2 G1, 2 G2), hyperbilirubinemia (1 G1, 1 G2), headache (3 G2), on PHS (1 G1), retinal toxicity (G2, protocol-specific scale, asymptomatic). TRAE at 10 mg/kg included: anemia (3 G1), headache (2 G1), and nausea (1 G1). Two patients with adenoid cystic carcinoma in Part A had stable disease for 16 and 8 months. In Part B, 2 of 3 patients have had prolonged stable disease at 10 mg/kg for 8+ months (follicular thyroid cancer) and 7+ months (myoepithelioma of the head and neck). Evaluation of subjects in the 20 mg/kg maintenance dose (ongoing). Conclusions: Hu5F9-G4 is well tolerated at 10 mg/kg weekly, with 1 mg/kg Priming Dose. Part B with a Maintenance Dose of 20 mg/kg is ongoing. Acknowledgements: Stanford Clinical and Translational Research Institute (Stanford University School of Medicine; Forty Seven, Inc. Trial Registration: NCT02164091. Willingham SB, et al. The CD47-signal regulatory protein alpha (SIRPa) interaction is a therapeutic target for human solid tumors. Proc Natl Acad Sci U S A. 2012 Apr 24;109(17):6662-7. 2. Liu J et al. Pre-Clinical Development of a Humanized Anti-CD47 Antibody with Anti-Cancer Therapeutic Potential. PLoS One. 2015 Sep 21(9):e0137345. References:


Figure: CD47 is a myeloid-specific immune checkpoint.
with chemotherapy and other targeted agents is also an important area of priority. The role of biomarkers to select therapy is another critical research priority. We should also make efforts to improve the percentage of patients enrolled in clinical trials. A major reason for this is the stringent eligibility criteria that excludes a significant proportion of patients in order to select the ‘fittest’ candidates for clinical trials. While this is certainly appropriate in early phase drug development, if patients enrolled in clinical trials do not represent the ‘real-world’ patient population, the applicability of the results are limited. The next wave of clinical trials should also take into consideration the impact of new treatments on the overall cost of care and the clinical significance of improvements in efficacy. The national Cooperative groups in the United States are committed to a collaborative approach to address research questions and improve outcomes for lung cancer.

**Keywords:** NSCLC, Adjuvant therapy, ALCHEMIST, immunotherapy

**SC15.04 THE JAPANESE PERSPECTIVE**
Yuichiro Ohe

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In Japan, several cooperative study groups, such as Japan Clinical Oncology Group (JCOG), West Japan Oncology Group (WJOG), North East Japan Study Group (NEJ), and Japan Clinical Oncology Cooperative Oncology Group (TCOG), Oncology Group in Kyushu (LOGiK), Okayama Lung Cancer Study Group (OLCSG) and so on are conducting investigator initiated cooperative clinical studies for lung cancer. Phase 3 studies are mainly conducted by JCOG, WJOG and NEJ. JCOG and WJOG are conducting intergroup phase 3 studies for lung cancer. More recently, multicenter phase 3 studies are also started. JCOG is a multicenter clinical study group for cancer treatment fully funded by the national research grants in Japan. The goal of the JCOG is to establish effective standard treatments for various types of malignant tumors by conducting nationwide multicenter clinical trials, and to improve the quality and outcome of the management of cancer patients. JCOG consists of 16 subgroups and JCOG Lung Cancer Study Group (JCOG-LCSG) consists of 44 institutions, was established in 1982. JCOG also have JCOG Lung Cancer Surgical Study Group (JCOG-LCSSG) established in 1986.

Only JCOG is supported by no industries but National Cancer Center and grants of Japan Agency for Medical Research and Development (AMED). Thus, JCOG studies are conducting completely independent from pharmaceutical companies. Other groups are supported by mainly pharmaceutical companies and grants of AMED. JCOG-LCSG has been conducting many randomized trials for small cell lung cancer and elderly non-small cell lung cancer. In case of JCOG-LCSG, protocol concepts are discussing in the group meeting held every 3 months. The protocol concept agreed in the group meeting will discuss in JCOG Protocol Review Committee and finally approved by JCOG Steering Committee. Kawano Y, Okamoto I, Fukuda H, et al. Current status and future perspectives of cooperative study groups for lung cancer in Japan. Respir Investig 52: 339-347, 2014.

**Keywords:** Japan Clinical Oncology Group, West Japan Oncology Group, Investigator initiated multicenter clinical study

**SESSION SC16: SUPERIOR SULCUS TUMORS**

**SC16.03 RADIOThERAPY FOR SUPTORn SCLNtS**

Maria Werner-Wasiak

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Superior sulcus tumors (SST) are unique among lung cancer in that they have a tendency for the invasion into the chest wall and a spread superiority outside the lungs, namely into the brachial plexus and the sympathetic chain, therefore causing a well-defined constellation of symptoms and signs, such as chest wall pain/shoulder pain, Horner’s syndrome, spinal cord compression, upper extremity edema etc. A primary surgical resection is rarely performed, and bi- or trimodality therapies are most often implemented, depending on tumor stage. A comprehensive evaluation of the tumor extent is mandatory before any intervention is undertaken. Following tumor biopsy to establish a diagnosis of non-small cell lung cancer, standard lung cancer staging studies need to be obtained, such as the chest and upper abdomen computerized tomography (CT) scan with intravenous contrast, a PET CT scan and contrast-enhanced brain imaging (CT or MRI). Routine blood work and pulmonary function testing are standard as well. However, there are two additional radiographic studies which are necessary for each superior sulcus tumor: (1) MRI scan of the cervical spine, brachial plexus, (2) MRI scan of the cervical and thoracic spine. The rationale for imaging the brachial plexus is not to confirm the plexus is invaded (which is evident based on the presenting symptoms and a physical examination), but rather to assess the degree of its vertical involvement, since only the lowest trunks of the brachial plexus can be safely resected without risk of permanent spine invasion, hence the need for the MRI, which provides a superior image quality than a chest CT scan. The overall treatment strategy depends on the nodal status (“N” stage). For those patients without nodal involvement (“N0”) or with involvement only of the ipsilateral hilar lymph nodes (“N1”), a common approach to use concurrent induction chemo-radiotherapy, followed by the surgical resection. If obvious mediastinal nodal involvement is seen (“N2 or N3”), the recommendation is for definitive concurrent chemo-radiotherapy without subsequent surgery. Therefore, invasive staging of the mediastinum, either with mediastinoscopy or with EBUS, is mandatory, since it may result in a change of therapy. The presence of chest wall invasion 

**Keywords:** superior sulcus tumor, Pancoast tumor, radiation therapy, Surgery
Background: Lung cancer is the leading cause of cancer deaths in the world. For patients with advanced non-small cell lung cancer (NSCLC), survival prognosis is very poor with chemotherapy and radiotherapy. However, the possibility of occult metastases may lead to discrepancy between clinical and pathologic staging and underestimation of the disease severity, and how to individualized choose the appropriate patients with locally advanced non-small cell lung cancer for surgery is controversies. In this study, we presented here the Chinese experience: individual precision surgery for locally advanced non-small cell lung cancer based on molecular staging. Methods: We developed several molecular biomarkers and molecular models from Circulation Tumor (CTC) detection, mi-RNA chip, Gene Chip from 1990. We used these Molecular biomarkers and molecular models for molecular staging, molecular typing, choosing indication of operation and neoadjuvant chemotherapy, predicting postoperative recurrence and prognosis of locally advanced non-small cell lung cancer. Results: We developed two molecular staging model for individualized surgical treatment for locally advanced non-small cell lung cancer involving heart, great vessels or both. 3308 patients with locally advanced non-small cell lung cancer were underwent completely resection of the cancer in the three medical center. The 1-, 3-, 5- and 10 year survival rate were 74.5%, 62.3%, 31.5% and 22.9%, respectively. We used our molecular staging model for neoadjuvant chemotherapy for 665 patients with locally advanced lung cancer. The 1-, 3-, 5- and 10-year survival rate were 79.35%, 57.31%, 48.79% and 39.98% of the patients, respectively. We used our molecular model to divide N2 lung cancer into invasive N2 and Non-invasive N2 group. We used our molecular models adenocarcinoma and squamous carcinoma to divide T4 lung cancer into high recurrence and low recurrence groups, and help postoperative adjuvant therapy. Conclusion: Our molecular staging and typing models can help us carry out individual precision surgery, predicting prognosis and cancer recurrence of the cancer for locally advanced non-small cell lung cancer. Keywords: non-small cell lung cancer, individual precision surgery, Molecular staging, molecular typing.
epidemiology study in newly diagnosed advanced lung adenocarcinoma, the EGFR active mutation rate is 50.2% in Chinese patient population. The incidence of EGFR mutations in patients who never smoked can be as high as 56.9%. ALK rearrangement is also common in this patient population. In a large cross-sectional study enrolled 1160 NSCLC patients, the incidence of ALK rearrangements is 8.1%. Noteworthy, 44% of patients younger than 30 years old harbor ALK rearrangements. However, genetic alterations test rate used to be low in China. According to a large national survey, the EGFR mutation test rate was only 20% in 2011. However, as the turnover time shortens, the testing fee decreases, and ctDNA testing becomes available, the EGFR/ALK assays have turned into routine practice in China. Moreover, NGS platforms detecting panels of mutations are commonly used in some leading centers now. 2. Novel agent availability There is severe delay in the approval for novel agents by Chinese FDA. For instance, Bevacizumab was approved by FDA for treatment of NSCLC in 2006, while it was approved by Chinese FDA 9 years later. To improve availability of novel agents, Chinese oncologists are active in participation in international multi-center clinical trials. In addition, more and more innovative drugs have been developed by domestic pharma industry and entered clinical trials (Table 3). Moreover, China FDA makes new policies to encourage innovative drugs and accelerating new drug application.

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<td>EGFR T790M Mutation</td>
<td>Phase I</td>
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<td>VEGFR-TKI</td>
<td>Nonsquamous NSCLC in 3L</td>
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<td>c-MET inhibitor</td>
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Table 1. Innovative drugs from China in clinical trials 3. Lung cancer prevention The incidence rate of lung cancer remains high in China between 2000 and 2011. Factors that have contributed to this issue include tobacco smoking and air pollution. 50% adult Chinese men were current smokers in 2010. In addition, smoking rates in adolescents and young adults are still rising in China. To reduce tobacco use in China, the government enacted a strict smoking control law in Beijing in June 2015. However, the air pollution is still a severe problem and needs to be improved urgently. 4. Economic burden There are several factors which have contributed to the heavy economic burden of lung cancer patients in China. First, the residents’ income is still low in China. In 2015, per capita disposable income (one year) was only $3300. Second, the cost of anti-cancer drugs is very high (Cisplatin/cycle $8500, Gefitinib/cycle $2200, Pemetrexed/cycle $3000, and Bevacizumab/cycle $5400). Moreover, only 20% of whole medical expense can be covered by insurance, and majority of targeted drugs can’t be covered.

Keywords: genetic alterations assays, lung cancer prevention, novel agents availability, economic burden

SC17.03 LUNG CANCER IN INDIA: CHALLENGES AND PERSPECTIVES

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Lung cancer is the commonest type of cancer in males and the leading cause of cancer death in both sexes worldwide. It is also the commonest in men in India accounting for 11.3% of all new cancers and also is the most common cause of cancer death (13.7%). In contrast to a decline trend in men in developed countries with a plateau for females, in India, the incidence continues to rise for both males and females. Data from the population based cancer registries developed under the National Cancer Registry Program of the Indian Council for Medical Research (ICMR) indicates that there is wide geographical variability in the incidence of this disease in different parts of the country. The highest age-adjusted incidence rates of 45 per 100,000 population are seen in the North-East region of India and are similar to areas reporting the highest incidence rates in some parts of the US and Europe. In other areas of India, especially the Western region, the age adjusted incidence rates are as low as 2 per 100,000 population. The demographic profile including age, gender, stage, histology and even the molecular epidemiology (prevalence of EGFR mutations and ALK rearrangements) varies considerably in different parts of India. However, the overall incidence is much lower than that compared to many western countries. The demographic profile of lung cancer seen in India needs special mention. In the past, a single-centre large series of 1009 patients presenting to our institute from 1977-86 had shown squamous histology to the commonest (34.3%) followed by adenocarcinoma (25.3%) and small cell lung cancer (SCLC; 20.3%). Subsequent analysis of 250 patients presenting to us three decades later (2007-09), we found that the histological pattern was largely unchanged with squamous still being the commonest (34.8%) followed by adenocarcinoma (26.0%) and SCLC (18.4%). The male-female ratio as well as the current/ex-smoker to never-smoker ratio was also similar between the two cohorts. A possible reason for the lack of change in demographic profile of lung cancer was thought to be related to the fact that ‘ bidi’ and NOT cigarette is the most common form of tobacco smoking in India. The ratio of bidi to cigarette smoking in India ranges from 2.5:1 to 7:1 in different parts of India and unlike cigarette making, there has been no change in the process of bidi manufacturing which is primarily a cottage industry. The other important aspect relates to its association of quantified tobacco exposure. The smoking index (SI; number of combined bids and cigarettes smoked per day multiplied by number of years smoked) has been developed for this purpose. Patients can be categorized as either never-smokers (SI=0), light to moderate smokers (SI=1-300) and heavy smokers (SI>300). In a cohort of 520 non-small cell lung cancer (NSCLC) patients, we observed that age, gender, histological type and stage differed significantly between the three groups. Never-smokers had significantly more females (52%), were younger (mean age 54.5 years), lesser squamous histology (28%), more advanced stage (IIIB/IV; 92%), more metastatic disease (67.4%) and more extra-thoracic metastases (62%) while group of heavy smokers had more males (98%), were older (mean age 61.2 years), more squamous histology (58%), lesser advanced stage (81%), lesser metastatic disease (39%) and lesser extra-thoracic metastases (17%). We have identified another risk factor in women to be heavy smoking. In a large cross-sectional study enrolled 1160 NSCLC patients, the incidence of approximately 83% of NSCLC histology at our centre) present with advanced stage (IIIB/IV) at the time of diagnosis and are managed non-surgically. Misdiagnosis as tuberculosis and empirical treatment with anti-tubercular drugs prior to referral to higher centre is one of the important causes for delayed diagnosis of this disease in India. Developpment of lung cancer in India need to be understood with regards to availability of health care and other resources necessary for appropriate management of the health related requirements of their population and this holds true for lung cancer as well. Some of the challenges in resource constrained settings include: Large population with high population density; illiteracy and poor health awareness; Sub-optimal economic and infrastructure inputs for health care; Suboptimal ratios of doctor and nurses for population; Overburdened hospitals and health care facilities; Huge burden of TB that hinders differentiation by the primary physician with lung cancer. Important issues in resource constrained settings is still the role of the non-platinum agent. Decision on dose intensity may also be influenced by similar factors (efficacy, tolerance, toxicity profile and packaging strengths of marketed drugs). A list of some of the important factors influencing decision are shown below.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Disease related</th>
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<tbody>
<tr>
<td>Age ++</td>
<td>Gender +</td>
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<tr>
<td>Histology +++</td>
<td>Molecular profile of tumor ++</td>
</tr>
<tr>
<td>Stage ++</td>
<td>Performance Status +++</td>
</tr>
<tr>
<td>Unrelated to disease</td>
<td>Medical reimbursement/insurance issues +++</td>
</tr>
<tr>
<td>+</td>
<td>Wishes of patient/family members ++</td>
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<tr>
<td>+</td>
<td>Frequency of hospital visits ++</td>
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SC17: LUNG CANCER: A GLOBAL CANCER WITH DIFFERENT REGIONAL CHALLENGES

TUESDAY, DECEMBER 6, 2016; 14:30-15:45
Lung cancer has been the most common cancer in the world for several decades. The number of new cases estimated in 2012 is 1.8 million cases (12.9% of the total), 58% of which occurred in the less developed regions. The disease remains as the second common cancer in man worldwide (1.2 million, 16.2% of the total) with the highest estimated rates in North America (33.8%) and Northern Europe (23.7%), a relatively high rate in Eastern Asia (19.2) and the lowest rates in Western and middle Africa (1.1 and 0.8 respectively).

In developing countries, lung cancer is the most common cancer among males and the third common cancer among females. Lung cancer is the most common cause of death from cancer worldwide estimated to be responsible for nearly one in 5 (1.59 million deaths, 19.4% of the total) (1). Temporal analyses reveal that significant reductions in lung cancer mortality have been observed in developed countries due to increased awareness of the harmful effects of smoking, asbestos and other factors. The role of early detection is also evident. (2). In contrast, lung cancer incidence and mortality rates have increased in some low and medium resource countries (3). The regional differences are mainly due to increased tobacco smoking in the developing countries, smoking waterpipe, cannabis or even passive and secondary smoke and in the meantime there is lack of tobacco control. There are also occupational risk factors such as asbestos exposure, dust, fumes, nickel, silica and insecticides and up till now there are areas that have not banned asbestos or succeeded to control occupational and environmental exposure and incidence as mesothelioma is increasing. (4) Many studies have shown that cases have genetic susceptibility to develop lung cancer specially in North Africa. Another important factor specially the Middle East North Africa is the increase in the elderly population that may be attributed to better infection control and improvement of general health care. As life expectancy continues to increase throughout the African continent, the burden of lung cancer is likely to increase. Given that an estimated 32,640 new lung cancer cases will be seen in Africa in 2015 (5). We have to remember also that cancer diagnosis rate in Africa is relatively low and patients present usually in an advanced stage so underreporting may be another factor. Accordingly, it is essential to know the magnitude of lung cancer in different regions in Africa by having cancer registry for the countries. So, obstacles to the global fight against lung cancer include lack of registry in some parts of Africa, low public awareness of lung cancer and absence of screening for the high risk cases, overburdened treatment centers and insufficient financial support. The way to combat these obstacles start from prevention and earlier detection in the low income countries. Public health awareness of the risk factors that cause lung cancer and the importance of avoiding smoking and banning asbestos should be clear and this is the role of public health agencies, media, and public media. The major tobacco companies should start and everyone should understand the danger of smoking.

This is done also by cooperation of scientific organizations of governmental and non governmental organizations. Also, we should reduce air pollution and regulate the occupational exposure of the employees to avoid the appearance of lung cancer and mesothelioma. As for early detection, screening can help in high risk patients and many authorities and NGOs can help to catch the early cases. In the meantime there should be ways to access modern imaging techniques to detect the cancer and use the minimal requirements for diagnosis and care. Accordingly it is essential to set the treatment guidance protocols to facilitate the management of the patients and to educate and train the doctors that should acquire degree granting programs and get certificates in the oncological field. It is mandatory to lower the cost of health care to encourage the patients to go for treatment and to get the proper care. There should be special dealing for the economic pressure and avoidance of financial toxicities for the patient. The last point that have to be ameliorated in Africa developing countries is research through international collaboration as studying genetic polymorphism and relation to smoking and changing patient concept about drugs received in clinical trials that use new drugs, proper investigations and lower the cost of treatment and may get better outcome. References 1- Globocan 2012 (IARC): Estimated cancer incidence, mortality and years lost worldwide according to International Comprehensive Cancer surveillance 2- Jemal A, Center MM, DeSantis C, Ward EM (2010) Global patterns of cancer incidence and mortality rates and trends. Cancer Epidemiol Biomarkers Prev 19:1893-1907. 3- Sankaranarayanan R, Jayant K, Brenner H (2011) An overview of cancer survival in Africa, Asia, the Caribbean and central America: the case for investment in cancer health services. IARC Sci Publ 257:291-6. 4- Gaafar RM, Eldin NH (2005) Epidemiologic of mesothelioma in Egypt. Lung Cancer 49: S1720. 5- Tao Z, Shi A, Lu C, Song T, Zhang Z, et al. (2014) Breast cancer: Epidemiology and Etiology. Cell Biochem Biophys.

Keywords: Lung cancer, cancer control, obstacles and perspectives, smoking

SESSION SC18: PRECISION SCREENING FOR LUNG CANCER TUESDAY, DECEMBER 6, 2016 - 16:00-17:30

SC18.01 FIELD CANCERIZATION IN THE AIRWAYS AND ITS APPLICATION TO LUNG CANCER EARLY DETECTION

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Molecular alterations that are characteristic of lung tumors have been shown to be present in normal-appearing lung airways adjacent to lung tumors suggestive of an airfield cancerization phenomenon (1, 2). These field effects include altered gene expression, loss of heterozygosity (LOH), gene mutation and methylation and microsatellite instability (3-7). Microarray studies have pointed to expression profiles that are dissimilar between airways in smokers with lung cancer and without lung cancer (8, 9). It has been recently demonstrated gene expression profiles that are shared between normal-appearing airway cells and nearby NSCLCs and that can distinguish airways of smokers with lung cancer from those without the malignancy (8). Studies from several groups suggest that the field cancerization provides critical insights into non-small lung carcinoma (NSCLC) ad small cell lung carcinoma (SCLC) pathogenesis and clinical opportunities for lung cancer detection (6, 10). It is important to note that smoking percutaenses inflammation throughout the exposed airway epithelium (10). This effect is pronounced in patients with Chronic Obstructive Pulmonary Disease (COPD) (10). Notably, among smokers, even after smoking cessation, airway inflammation persists while the risk of lung cancer continues to increase (10). It is not known which tumor promoting profiles in the airway field cancerization may drive lung cancer development in COPD patients. Using microarray profiling, studies have pointed to expression profiles that are dissimilar between airways in smokers with lung cancer and airways in smokers without cancer (11-13). Importantly, these gene-expression changes within the “field of injury” have been leveraged for development and validation of a clinically-relevant biomarker that can improve the diagnostic performance of bronchoscopy for detection of lung cancer (predominantly NSCLC) among smokers with suspect disease (8, 12). In addition, gene expression array analysis pointed to airway field expression profiles that are spatially and temporally modulated in early stage patients following surgery and that may be associated with disease relapse (13). Further, we have recently demonstrated that there is significant enrichment of gene expression profiles measured in both small (adjacent to tumor) and large (mainstem bronchus) airway compartments of the airway field of injury, suggesting that gene-expression changes in the large airway can serve as a surrogate for the molecular changes occurring in the primary epithelial adjacent to the tumor (9). Taken together, studies from our group and others suggest that, by sampling “normal” and relatively accessible tissue (e.g., bronchial airway), the airway field of injury provides biological insights into the earliest phases in the development of lung malignancy and potential valuable clinical opportunities for early detection. Thus, specific molecular aberrations that precede cellular morphological changes will provide biological insights into why some smokers develop lung cancer and, thus, clinical opportunities for improved lung cancer detection. References: 1. Kadara H, Wistuba II. Field cancerization in non-small cell lung cancer. Implications in disease pathogenesis. Proceedings of the American Thoracic Society. 2012;9(2):38-42. 2. Steiling K, Ryan J, Brody JS, Spira A. The field of injury in the lung airway. Cancer Prev Res. 2008;1(6):396-403. 3. Belinsky SA, Nikolaj KJ, Palmisano WA, Michels R, Saccamanno G, Gabrielson E, Baylin SB, Herman JG. Aberrant methylation of p16(INK4a) is an early event in lung cancer and a potential biomarker for early diagnosis. Proc.
could be used in a risk assessment evaluation for screening programs. We will do we prevent the overdiagnosis bias? Here we focus on biomarkers that NLST without causing more harm than good? Once the CT screening studies for limited detection relates to how many at-risk individuals are studied with can be sufficient to cause a stage shift and therefore improve outcome. Finally, it to develop more accurate individual and cumulative risk estimates for specific diseases. We should therefore consider a joint effects approach to determine individual biomarker associations as well as to ascertain the impact of simultaneous increases in multiple biomarker concentrations on the diagnosis of lung cancer. Biomarkers of risk would ideally be tested prospectively in a randomized clinical trial. However, given the relatively low prevalence of this disease, the number needed to screen may be prohibitive; therefore the benefits of precision screening? Are current risk prediction models safe to use or robust to guarantee an advantage over current standard of care? There is a clear need to evaluate the benefit of risk assessment biomarkers with repeated measures over time. The assumption is that as risk increases, molecular moieties should be more readily available (e.g. in the circulation) over time. This situation is true for tumor specific antigens and ctDNA, but would not apply to genetic risk. Statistical models could test the ability of different biomarkers to complement each other in a single population, in order to eventually determine those that could be tested prospectively. Given biomarkers’ non-specificity and commonality in predicting diseases, modeling multiple markers at the same clinical diagnostic criteria can be used to develop more accurate individual and cumulative risk estimates for specific diseases. Low-dose computed tomography for high-risk individuals has for the first time demonstrated unequivocally that early detection save lives. The currently accepted screening strategy comes at the cost of a high rate of false positive findings while still missing a large percentage of the cases. Therefore, there is increasing interest in developing strategies to better estimate the risk of an individual to develop lung cancer, to increase the sensitivity of the screening process, to reduce screening costs and to reduce the number of individuals harmed by screening and follow-up interventions. New molecular biomarkers candidates show promise to improve lung cancer outcomes. This review discusses the current state of biomarker research in lung cancer screening with the primary focus on risk assessment. The rationale for developing biomarkers for the early detection of lung cancer is very strong and well established. It stems from the fact that, at the population level, the earlier we detect the disease, the better the outcome and the lower the health care cost. The impetus for biomarker development has grown stronger since the NLST trial demonstrated that early detection via chest CT screening reduced the relative risk for lung cancer death in the high risk individuals. Low dose chest CT in this group alone may save up to 12,000 lives a year, but it represents only about 8% of individuals dying of this disease every year. Thus, much is to be done to capture these lung cancers that escape chest CT screening as currently recommended despite its high sensitivity and specificity. The reason for limited detection relates to how many at-risk individuals are studied with CT and to how we best define this risk. Detection and careful management of indeterminate pulmonary nodules are integral parts of this effort. Lung cancer screening using chest CT also raises many questions, some of which could be addressed with well poised biomarkers. For example, who is at utmost risk for lung cancer? How do we expand the screening criteria from the NLST without causing more harm than good? Once the CT screening studies are done, how do we diagnose lung cancer? How do we prevent the overdiagnosis bias? Here we focus on biomarkers that could be used in a risk assessment evaluation for screening programs. We will discuss current molecular biomarkers of risk assessment in those without measurable disease and before a chest CT has been done. Consideration of the use of such biomarkers should trigger a discussion with the patient before ordering it to address the intent of the test and the implications of the possible results. Many biomarkers have been developed over the years to predict tumor development. Let us consider the characteristics of such a biomarker to assess the risk of lung cancer. For screening purposes, given the low prevalence of disease, a strong negative predictive value (NPV) of a test is a very attractive feature. High specificity on the other hand is always desirable so we do not overcall cancers (false positive). Should such a test be positive, it would push individuals into a higher risk group to consider appropriate surveillance. The biomarker could measure a genetic risk (e.g. altered metabolism of carcinogens, DNA repair machinery abnormalities, predisposition to inflammation, or germline mutations) or the influence of the environment on tumor development (e.g. exposure to carcinogens or surrogates of risk such as epigenetic changes in the airway epithelium or the prevalence of preinvasive lesions). There has been recent interest in the potential for genetic variants to give insight into the pathogenesis of lung cancer. These variants indicate that there is great heterogeneity in mechanisms of disease development that is modulated by inherited genomic variation. With these come the opportunity to improve models predicting lung cancer risk. A larger question of timeliness of biomarker use in clinical practice will be discussed during the presentation. What are the risk and benefits of precision screening? Are current risk prediction models safe to use or robust to guarantee an advantage over current standard of care? There is a clear need to evaluate the benefit of risk assessment biomarkers with repeated measures over time. The assumption is that as risk increases, molecular moieties should be more readily available (e.g. in the circulation) over time. This situation is true for tumor specific antigens and ctDNA, but would not apply to genetic risk. Statistical models could test the ability of different biomarkers to complement each other in a single population, in order to eventually determine those that could be tested prospectively. Given biomarkers’ non-specificity and commonality in predicting diseases, modeling multiple markers at the same clinical diagnostic criteria can be used to develop more accurate individual and cumulative risk estimates for specific diseases. We should therefore consider a joint effects approach to determine individual biomarker associations as well as to ascertain the impact of simultaneous increases in multiple biomarker concentrations on the diagnosis of lung cancer. Biomarkers of risk would ideally be tested prospectively in a randomized clinical trial. However, given the relatively low prevalence of this disease, the number needed to screen may be prohibitive; therefore the development of registries is most appropriate. Registries are longitudinal cohort prospective studies where a biomarker is introduced but does not force providers to change their management. The lead time to diagnosis may be sufficient to cause a stage shift and therefore improve outcome. Finally, it is through better understanding of the biology of cancer development and of preinvasive lesions that we will shed further light into the field of biomarker research.
With that of the US National Lung Screening Trial (NLST), which has published an estimate of $81,000 per quality-adjusted life-year (QALY) as its mean incremental cost-effectiveness ratio (ICER) [7]. All UKLS cost estimates were based on 2011-12 NHS tariffs (Costs provided in £ £1=£1.5 on 30-11-15). Owing to the brief duration of the trial, observations relevant to economic evaluation were limited to cost-incurring events associated with screening and the initial management of screen-detected cancers. Expected outcomes of the cancers detected were simulated on the basis of both life tables and published survival data from other studies. The costs incurred from UKLS are of endobronchial ultrasonography (EBUS) in 1994. EBUS using a guide sheath (EBUS-GS) also began in 1996 of patent blood vessels, patent bronchi, hemorrhage, calcification, dilated bronchi, necrosis, and small amounts of air in alveoli. 3) EBUS using a guide sheath (EBUS-GS) 1,2 The GS-covered probe is advanced to the PPL, then after confirmation by EBUS that the lesion has been reached, the probe is removed before inserting the brush and biopsy forceps through the GS that is held in place in the lesion. This technique enables cytology and biopsy to be performed several times with minimal risk of bleeding. 4) Insertion of the bronchoscope (saline immersion technique) After observing the bronchial lumen, the bronchoscope should be advanced while visualizing the branches to the bronchus near the peripheral lesion. Upon reaching a position where further advancement is not possible, flushing of 1-ml saline (total 5-10 ml) several times is performed through the working channel of the bronchoscope. This is done to fill the bronchus, remove any sputum, and visualize the lumen. The GS-covered probe is then inserted from the working channel into the bronchus. In cases of ground glass nodule (GGN), we do not perform the saline immersion technique. Benign lesions are hyperechoic points which resemble EBUS image of GGN. 5) EBUS visualization The operator advances the US probe from the working channel of the 4-mm bronchoscope towards the periphery and stops when some resistance is felt. The duration of X-ray fluoroscopy should be limited as much as possible; also, an iris of the fluoroscopy machine should be used to limit X-ray exposure. The GS-covered probe is advanced to the PPL, then after confirmation by EBUS that the lesion has been reached, the probe is removed before inserting the brush and biopsy forceps through the GS. Asano et al.1,2,3 reported that the diagnostic yield by EBUS-GS and VBN was between 63.3% and 84.4% in reports on VBN for PPLs searched in PubMed as of November 2011. When the ultrasound probe is advanced to the bronchus near the peripheral lesion, the EBUS image is called “adjacent to”. In this case, we could change the direction of the tip of the bronchoscope using the up and down lever of the bronchoscope under fluoroscopy. We select the direction of the tip of the bronchoscope using the up and down lever of the bronchoscope under fluoroscopy. We select the direction of the tip of the bronchoscope using the up and down lever of the bronchoscope under fluoroscopy. We select the direction of the tip of the bronchoscope using the up and down lever of the bronchoscope under fluoroscopy. We select the direction of the tip of the bronchoscope using the up and down lever of the bronchoscope under fluoroscopy. We select the direction of the tip of the bronchoscope using the up and down lever of the bronchoscope under fluoroscopy. We select the direction of the tip of the bronchoscope using the up and down lever of the bronchoscope under fluoroscopy. We select the direction of the tip of the bronchoscope using the up and down lever of the bronchoscope under fluoroscopy. We select the direction of the tip of the bronchoscope using the up and down lever of the bronchoscope under fluoroscopy. We select the direction of the tip of the bronchoscope using the up and down lever of the bronchoscope under fluoroscopy.
Keywords: bronchoscopy, peripheral pulmonary lesion, guide sheath, EBUS

SC19: INTERVENTIONAL PULMONOLOGY IN DIAGNOSIS AND TREATMENT OF THORACIC MALIGNANCIES
TUESDAY, DECEMBER 6, 2016 - 16:00-17:30

SC19.02 INVASIVE STAGING OF LUNG CANCER: EBUS, EUS AND BEYOND
Kazuhiro Yasufuku
Division of Thoracic Surgery, Toronto General Hospital, University of Toronto, Toronto/ON/Canada

Despite the advances in surgical treatment and multimodality treatment, lung cancer is still the leading cause of death from malignant disease worldwide. Accurate staging is important not only to determine the prognosis but also to decide the most suitable treatment plan. During the staging process of non-small cell lung cancer (NSCLC), mediastinal lymph node staging is one of the most important factors to determine the outcome. Non-invasive staging such as computed tomography (CT) and positron emission tomography (PET) indicate size and metabolic activity, respectively. However imaging alone is inaccurate and therefore tissue sampling is the preferred and most reliable. Surgical staging by mediastinoscopy has been the gold standard for mediastinal lymph node staging but requires general anesthesia and complications cannot be ignored. Endoscopic ultrasound techniques provide a minimally invasive alternative for surgical staging. The current available endoscopic ultrasound techniques for mediastinal staging include transesophageal endoscopic ultrasound guided fine needle aspiration (EUS-FNA) and endobronchial ultrasound guided transbronchial needle aspiration (EBUS-TBNA). Both procedures can be performed in an outpatient setting under local anesthesia. EUS-FNA is a sensitive and safe method of evaluating the inferior mediastinal nodes (stations 7, 8, and 9), while EBUS-TBNA is preferred for evaluation of the anterior mediastinal nodes (n=3 and n=6) as these nodes are accessible from the esophagus. However, in spite of the strength of EUS-FNA for evaluating the inferior mediastinal nodes, its ability to evaluate lesions anterior to the trachea is limited. On the other hand, EBUS-TBNA has reach to the paratracheal and subcarinal (stations 2K, 4L, 4L, 7), as well as the N1 lymph nodes (stations 10,11,12). EBUS can be used through the esophagus for a EUS-like approach to the inferior mediastinal lymph nodes. Thus, EUS-FNA and EBUS-TBNA are complementary methods for lymph node staging in lung cancer and most of the mediastinum and the hilum can be evaluated with these endoscopic procedures. Aortic nodes (stations S1 and S6) are exceptions and must be evaluated by surgical methods. (anterior mediastinotomy, VATS, thoracotomy).

Based on the current evidence, EBUS-TBNA and EUS-FNA presents a minimally invasive endoscopic procedure as an alternative to mediastinoscopy for mediastinal staging of NSCLC with discordant N2 or N3 lymph node enlargement, provided negative results are confirmed. In surgical settings EBUS-TBNA can access all lymph nodes available by mediastinoscopy as well as hilar (N1) lymph nodes. EUS-FNA has access to the inferior mediastinal lymph nodes not accessible by mediastinoscopy. EBUS-TBNA and/or EUS-FNA have in fact replaced mediastinoscopy in many patients with diffuse mediastinal adenopathy, where a simple tissue diagnosis is required to determine treatment. When combined the techniques offer safe and accurate assessment of mediastinum, with accuracy surpassing that of the pinnovous gold standard – cervical mediastinoscopy. EBUS-TBNA and/or EUS-FNA can also be repeated with ease and have been used for mediastinal restaging in patients who underwent neoadjuvant therapy in preparation for definitive surgery intervention. Ultrasound image analysis of lymph nodes may assist bronchoscopists during EBUS-TBNA or EUS-FNA. Standard sonoanographic classification of lymph nodes can help characterize mediastinal and hilar lymph nodes as benign or malignant, which may guide the decision on which lymph nodes to biopsy. Newer imaging technology such as elastography can potentially enhance US guided image analysis of the lymph nodes.

Keywords: lung cancer, bronchoscopy, palliation

SESSION SC20: SMALL IS BEAUTIFUL: IMPACT OF SURGICAL APPROACH
TUESDAY, DECEMBER 6, 2016 - 16:00-17:30

SC20.01 MUSCLE SPARING THORACOTOMY: CAN IT STILL BE CONSIDERED A STANDARD?
Clemens Aigner
Thoracic Surgery, Ruhrlandklinik University Clinic Essen, Essen/Germany

Muscle sparing thoracotomy has a standard approach in thoracic surgery for a long time. Minimal invasive approaches have gained a widespread acceptance recently and were included in the treatment guidelines for early stage NSCLC by several societies. Prospective randomized trials comparing minimal invasive approaches versus muscle sparing thoracotomy in stage I NSCLC have already been performed more than twenty years ago and demonstrated equal morbidity and mortality. Nevertheless it took until 2013 that the American College of Chest Physicians guidelines recommended a VATS approach for clinical stage I NSCLC over a thoracotomy in experienced centers (1). No recommendation is made for more advanced stages. When analyzing national registry data still a high percentage of procedures in performed in an open way. This means that in current practice thoracotomy is still used as a standard approach by many surgeons. Minimal invasive approaches – both videothoracoscopic and robotic – are not different operations but different approaches towards performing an operation. It has been proven in several studies that in early stage lung cancer minimal invasive approaches in its various form lead at least to equivalent or even better oncologic outcome compared to an open approach. Nevertheless in more advanced stages this proof is lacking. Experienced centers reported individual series of minimal invasive approaches towards advanced procedures such as sleeve resection, pneumonectomy, chest wall resection and Pancoast tumor resection. While these technically feasible no data on long-term outcome of larger patient cohorts are available and an open approach is considered standard in these cases. Thus for tumors with invasion of hilar structures or sleeve resection a muscle sparing thoracotomy currently remains a standard approach. Perceived advantages of minimal invasive approaches – VATS as well as RATS – include less pain, fewer complications, shorter length of stay, faster return to normal activity and higher rate of adjuvant chemotherapy compliance. There are a few single center studies challenging these assumptions (2,3) as well as a recent analysis of Danish national data (4), however the majority of studies are in favor of minimal invasive approaches. A summary of muscle sparing thoracotomy remains a standard approach for advanced stage tumors, whereas early stage lung cancer should be treated minimally invasive in experienced centers. References 1) Detterbeck FCI, Lewis SZ, Diekemper R, Addrizzo-Harris D, Alberts WM. Executive Summary: Diagnosis and

SC20.02 WHAT HAVE WE ACHIEVED? SHOULD IT BE PERFORMED FOR STAGES HIGHER THAN STAGE I DISEASE?
Tomasz Grodzki
Pomeranian Medical University, Department of Thoracic Surgery and Transplantation, Szczecin/Poland

Since the introduction of the videothoracoscopic anatomical lung resections in the early 90-ties both indications and contraindications for this type of approach have changed dramatically (1, 2). There is common agreement that the oncological principles during surgery for lung cancer have to be the same regardless the type of approach: standard, minimal invasive (MIS – VATS), multiportal or uniporal, intubated or non-intubated) or robotic. It regards predominantly requirements such as careful andatraumatic dissection, sufficient free-of-neoplasm margins and proper lymphadenectomy (standard or extended). Keeping it in mind we have to admit that stage I NSCLC seems „unnecessary“ for MIS, particularly for early stages experienced surgeons. This type of surgery (MIS for stage I) is widely accepted and performed worldwide in thousands of cases. However, many experienced centers and surgeons have moved the borders forward treating more advanced cases by MIS with acceptable results regarding complications, mortality, conversion rate or quality of lung functional recovery. Gonzalez-Rivas SC et al. In the series of 63 advanced patients (tumors bigger >5 cm, T3 or T4, treated by neoadjuvant chemo- or radiotherapy) who were treated by uniporal VATS with good results comparable with earlier stages (3). Authors stated that „Skilled VATS surgeons can perform 80% or more of their lobectomies thoracoscopically, reserving thoracotomy only for huge tumors or complex bronchovascular reconstructions”. Large multicenter series of more than 400 advanced cases treated by VATS approach compared with propensity score matched open thoracotomy group with no differences in overall survival was published by Cao et al. (4). According to the VATS Consensus Statement (among 50 international experts to establish a standardized practice of VATS lobectomy after 20 years of clinical experience) eligibility for VATS lobectomy should include tumors <7cm and N0 or N1 status. Chest wall involvement was considered contraindication while centrity of tumour was considered a relative contraindication when hilar structures are preserved. The same incision, Uniportal VATS can pose a challenge for both the surgeon and the assistant. The surgeon and the assistant should be positioned in front of the patient in order to have the same thoracoscopic vision during all steps of the procedure and experience more coordinated movements. Even though the field of vision may be still limited in the upper anterior space, the combined movements of the thoracoscope along the incision will create different angles of vision (in this context, a 30 degree thoracoscope is recommended to achieve a panoramic view). The advantage of using the thoracoscope in coordination with the instruments is that the vision is directed to the target tissue and by using the instruments directly towards the hilum so that there is a smaller angle for the stapler to pass without impinging on the structures behind. Even if the wound is sited too high – in the 4th intercostal space for an upper lobectomy – the dissection of the hilar vessels may be easier, but the instruments enter directly towards the hilum so that there is a smaller angle for the stapler to pass without impinging on the structures behind. When the lobectomy is complete, the lobe is removed in a protective bag and a systematic lymph node dissection. For most of the surgical steps the thoracoscope is usually placed at the posterior part of the utility incision working with the instruments in the anterior part. For lower lobectomies the normal sequence of dissection is as follows: inferior pulmonary ligament, inferior pulmonary vein, pulmonary artery, bronchus and finally completion of the fissure. In case of upper lobectomies, the pulmonary artery is normally divided first, followed by vein, bronchus and fissure. When the lobectomy is completed, the lobe is removed in a protective bag and a systematic lymph node dissection is accomplished. The intercostal spaces are infiltrated with bupivacaine at the end of the procedure. A single chest tube is placed in the posterior part of the incision. We do not routinely employ epidural or paravertebral catheters. Future current improvements such as the specifically designed surgical instrumentation with double articulation, improvements in high definition video-camera systems, new energy devices and more narrower and angulated curved tip staplers have made single-port VATS, for major lung resections, easier to adopt and learn than conventional VATS. The demonstrated benefits of geometrical characteristics of the technique enable expert surgeons to perform complex cases and reconstructive techniques, such as broncho-vascular procedures or even carinal resections. The future of the thoracic surgery is based on the evolution of minimally invasive procedures and innovations directed towards reducing even more the surgical and anesthetic trauma. We can expect more developments of subcostal or embryonic natural orifice

SC20.04 UNIPORTAL VATS
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Introduction Uniportal video-assisted thoracic surgery (VATS) has been established as an alternative surgical approach for the treatment of most intrathoracic conditions. The potential benefits of a better view, anatomic instrumentation, better cosmesis and potential less postoperative pain and paraesthesia have led this approach to become of increasing interest worldwide. Performing surgery through a single incision approach represents an extension of VATS to a less invasive approach. The early period of uniporal VATS development was focused between the mid- and the second phase uniporal VATS started in 2010 with the development of the technique for major pulmonary resections. The creation of specific uniporal VATS programs in high volume centers like the Shanghai pulmonary hospital (the bigger thoracic program in the world with over 1000 major pulmonary resections per year) has contributed to spread out the technique to a large number of surgeons from all over the world in a short period of time. Surgical technique Uniportal VATS represents a radical change in the approach to lung resection compared to the conventional three-port VATS. Since the placement of the instruments and the camera is done through the same incision, Uniportal VATS can pose a challenge for both the surgeon and the assistant. The surgeon and the assistant should be positioned in front of the patient in order to have the same thoracoscopic vision during all steps of the procedure and experience more coordinated movements. Even though the field of vision may be still limited in the upper anterior space, the combined movements of the thoracoscope along the incision will create different angles of vision (in this context, a 30 degree thoracoscope is recommended to achieve a panoramic view). The advantage of using the thoracoscope in coordination with the instruments is that the vision is directed to the target tissue and by using the instruments directly towards the hilum so that there is a smaller angle for the stapler to pass without impinging on the structures behind. When the lobectomy is too low, there may be a good angle for the stapler to pass, but the distance to the hilum becomes too great. When the lobectomy is too low, there may be a good angle for the stapler to pass, but the distance to the hilum becomes too great. The air in which instruments can be placed towards the hilum becomes too narrow – leading directly between the instruments and camera. The incision itself is typically 3-4cm long, although longer incisions can be used (e.g. for an inexperienced surgeon, large tumor, thicker chest wall, etc) without any obvious disadvantage to the patient. It is helpful to olate the surgical table away from surgeons during the hilar dissection and division of structures, and towards the surgeons for the lymph node dissection. For most of the surgical steps the thoracoscope is usually placed at the posterior part of the utility incision working with the instruments in the anterior part. For lower lobectomies the normal sequence of dissection is as follows: inferior pulmonary ligament, inferior pulmonary vein, pulmonary artery, bronchus and finally completion of the fissure. In case of upper lobectomies, the pulmonary artery is normally divided first, followed by vein, bronchus and fissure. When the lobectomy is completed, the lobe is removed in a protective bag and a systematic lymph node dissection is accomplished. The intercostal spaces are infiltrated with bupivacaine at the end of the procedure. A single chest tube is placed in the posterior part of the incision. We do not routinely employ epidural or paravertebral catheters. Future current improvements such as the specifically designed surgical instrumentation with double articulation, improvements in high definition video-camera systems, new energy devices and more narrower and angulated curved tip staplers have made single-port VATS, for major lung resections, easier to adopt and learn than conventional VATS. The demonstrated benefits of geometrical characteristics of the technique enable expert surgeons to perform complex cases and reconstructive techniques, such as broncho-vascular procedures or even carinal resections. The future of the thoracic surgery is based on the evolution of minimally invasive procedures and innovations directed towards reducing even more the surgical and anesthetic trauma. We can expect more developments of subcostal or embryonic natural orifice
transluminal endoscopic surgery access, evolution in anaesthesia strategies, and cross-discipline imaging-assisted lesion localization for single-port VATS procedures. Improvements in anaesthetic techniques such as non-intubated or awake unilateral VATS may further quicken postoperative recovery allowing the tumor resection to be performed in an ambulatory setting. Furthermore, the need to reduce the risk of intercostal nerve damage associated with the transthoracic incision has led to the recent development of unilateral subxiphoid VATS technique for major pulmonary resections. We truly believe that with the unipolar approach, combined with yet-to-come 3D image systems (adapted on the screen, no glasses) and single port robotic technology and wireless cameras in awake patients. We understand that the future goes in the direction of digital technology which will facilitate the adoption of single-port technique worldwide in the next coming years.

Keywords: Thoracoscopy, lung cancer surgery, unilateral VATS, lobectomy

SESSION SC21: PREDICTIVE BIOMARKERS FOR OUTCOME OF SYSTEMIC THERAPY IN NSCLC
TUESDAY, DECEMBER 6, 2016 - 16:00-17:30

SC21.04 PATIENT-DERIVED XENOGRAFTS FOR GUIDING THERAPY OF LUNG CANCER
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Preclinical drug screening and biomarker discovery in the NCI-60 cancer cell line panel as well as the xenograft developed by growing these cell lines subcutaneously in immunodeficient mice have repeatedly failed to predict clinical responses. In an attempt to circumvent the limited predictive values of conventional preclinical models, there has been increasing attention in the development and characterization of Patient-derived tumor xenograft (PDX) models. The PDX models, which were created by direct implantation of patient’s tumor in immunodeficient mice, have shown to reflect principal histologic and genetic characteristics of original patient tumors and retain tumor heterogeneity better than any other preclinical model. These models have been shown to be predictive of clinical outcomes and are being used for translational research, preclinical drug screening and biomarker identification and validation. The PDX model may also be used in the application of ‘co-clinical trial’ approach, in which it is developed from a patient enrolled in a clinical trial and treated with the same experimental agents to emulate clinical response. This strategy permits the assessment of drug response simultaneously in the patient and mouse model, providing an interesting platform to investigate resistance mechanisms, predictive biomarkers and novel combination strategies in a real-time manner. I will present the utility of PDX models, which faithfully replicated the histologic, genomic and pharmacologic features observed in the original patients, and ‘co-clinical trial’ that mirror a phase II trial of agents targeting fibroblast growth factor receptor (FGFR) in non-small cell lung cancer.

Keywords: Predictive biomarker, patient-derived tumor xenograft, co-clinical trial

SESSION SC22: SELECTION AND MONITORING OF PATIENTS FOR IMMUNE CHECKPOINT INHIBITORS
TUESDAY, DECEMBER 6, 2016 - 16:00-17:30

SC22.01 HOW DO I DEFINE OPTIMAL CANDIDATES FOR IMMUNOTHERAPY IN MY PRACTICE?
Johan Vansteenkiste1, Els Wauters2
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Over the recent decade, we witnessed important progress in the treatment of patients with advanced NSCLC in three domains. First, cytotoxic chemotherapy, where histology-directed chemotherapy with cisplatin–pemetrexed, followed by pemetrexed maintenance therapy in appropriate candidates, has resulted in a median overall survival (OS) of 16.3 months in adenocarcinoma [1]. Second, the use of tyrosine kinase inhibitors (TKIs) in tumors driven by specific molecular pathways, such as EGFR, ALK and others, has largely improved progression-free survival (PFS) compared to the one with chemotherapy in randomized studies, and had led to OS times of several years in many of these patients [2]. Third, immunotherapy with immune checkpoint inhibitors (ICI) directed against the immunosuppressive molecules programmed cell death 1 (PD-1) and programmed cell death ligand 1 (PD-L1) has been in clinical trials since 2009. At present, the anti-PD-1 antibodies nivolumab (a fully human IgG4 antibody) and pembrolizumab (a humanized IgG4 antibody) have been approved by NSCLC by different regulatory agencies worldwide. EMA approved nivolumab for advanced NSCLC after prior chemotherapy, and pembrolizumab for advanced NSCLC in adults whose tumors express PD-L1 and who have received at least one prior chemotherapy regimen. At present, the choice of writing this text but there were no public randomized study data on the use of these agents in in line therapy, we will therefore concentrate on the relapse therapy setting. Despite the real progress made by ICI therapy, we must realize that at present only about 20% of the patients respond to single-agent ICI treatment, while 50% have early progression (Checkmate 017 [3]; Checkmate 057 [4]). Moreover, the cost of these drugs is considerable. Hence it is important to define optimal candidates in clinical practice. Elements in this decision are a) clinicopathological factors; b) possible predictive biomarkers; and c) the availability of other treatment choices. As for a) clinicopathological factors, there is no evidence that age, gender or ethnicity determine activity of ICIs. Smoking history, on the other hand, is strongly associated with better response rate to ICI therapy. Although EGFR oncogene pathway activation has been linked to upregulation of PD-L1 in tumor cells, response rates to ICIs in these patients are generally reported to be lower. In e.g. Checkmate 057, the overall response rate was 19%. It was 22% in smokers vs. 9% in non-smokers, 18% in EGFR-wildtype vs. 11% in EGFR-mutant tumors. Further understanding and refinement of the use of ICIs in tumor with an oncogene driven is needed. (b) A multitude of potential predictive biomarkers of response to PD-1/PD-L1 pathway inhibitors has been reported. In particular, PD-L1 expression in tumor and/or immune cells, the presence of TILs (tumor-infiltrating lymphocytes, CD8+ T-cells in particular), and the overall mutational load in the tumor cells have been linked to activity of ICIs [5]. PD-L1 expression on tumor cells, determined by immunohistochemistry (IHC) staining is by far the one most close to clinical practice for selecting optimal candidates for immunotherapy. This biomarker is more powerful than e.g. EGFR/HER2 mutation as predictor of efficacy of EGFR TKIs. EGFR mutation is limited to certain NSCLC histologies and is only one of the many checkpoints in a complex interaction, and is a gradual phenomenon. Nonetheless, as can be noted from the pictures in this presentation, in metastatic phase III studies such as Checkmate 017 – PD-L1 IHC predicts efficacy of ICI therapy. We added the large phase I study Keynote 001 to the figure as a very illustrative example: Over the categories of PD-L1 expression, response rate increased from 8% in the lowest to 45% in the highest category [6]. In the Keynote 010 phase III study, the hazard ratio of OS versus chemotherapy was 0.76 in the low-, but 0.54 in the high-expression group [7]. In the Checkmate 057, the OS hazard ratio even was 1.00 in all patients with tumors having PD-L1 <10%. Thus, except for the Checkmate 017 dataset, PD-L1 IHC enriches the response rate and differential OS benefit vs. chemotherapy, and can be used to stratify these expensive agents to the optimal candidates. Dacetaxel single-agent chemotherapy was the comparator in the phase III studies on relapse therapy. In the meanwhile, progress has been made in conventional relapse therapy as well. In the LUME-Lung 1 trial, the combination of docetaxel and the triple angiogenesis inhibitor nintedanib resulted in a significantly better OS than docetaxel alone [8]. We agree that there is a difference in OS of 2.3 months – 6 months – in patients with adenocarcinoma [8]. In the REVEL study, patients treated with docetaxel plus ramucirumab, a VEGF receptor 2 inhibiting monoclonal antibody, had significantly better OS than those treated with docetaxel alone across all NSCLC histologies [9]. In conclusion, the choice of ICI therapy for relapsing NSCLC needs to be considered in the available treatment options for these patients, and this can be based on clinicopathological factors, predictive biomarkers, and comparison of efficacy of various treatments in specific subgroups. While PD-L1 is not a biomarker with the strength such as e.g. EGFR mutation, it helps to optimize the response rate and differential OS benefit of ICI therapy vs. chemotherapy, and to can be used to designate these expensive agents to the optimal candidates. See Figure below.

Keywords: Real-world practice, Immunotherapy, PD-L1

SC22.03 HOW DO I MONITOR FOR AND TREAT IMMUNE-RELATED EVENTS? Alexander Spira Virginia Cancer Specialists Research Institute, Virginia Cancer Specialists, Fairfax/VA/United States of America

Immunotherapy (IT) has become one of the most potent new treatments for all cancers, particularly non-small lung cancer. However, it has a unique toxicity profile different than most therapies (chemotherapy; biologic; targeted therapy) than most oncologists are familiar with, specifically immune related adverse events; irAE. These toxicities may be acute but can also occur weeks and months after starting or even stopping therapy. Given the prolonged duration that patients may be exposed to these drugs, they become important to monitor over a short and long period. Further, given the responses and the relative milder toxicity compared with traditional chemotherapy agents, the older patient population may be exposed to these agents at a somewhat higher frequency. The use of immunomodulatory drugs to counter irAE toxicity will be discussed as to how it affects efficacy of immunotherapy. This lecture will focus on:

- Timeframe and monitoring for immune-related toxicity (with special attention paid towards pulmonary, gastrointestinal and endocrinopathies) using the appropriate immunosuppressive drugs
- Management of toxicities related to IT
- Decision making on re-exposure to drug after irAE
- Patient education
- Toxicities associated with combination IT drugs that may be used in the future or on clinical trials

Keywords: Immunotherapy, adverse events

SC22.04 HOW CAN IMMUNOTHERAPY BE IMPLEMENTED IN A COST-EFFECTIVE STRATEGY? Christoph Zielinski

Department of Medicine I and Comprehensive Cancer Center, Medical University Vienna, Vienna/Austria

When talking about immunotherapy and its cost-effectiveness, the story of disharmony between the magnitude of clinical benefit and the cost-effectiveness of certain drugs clearly emerges. I will try to illustrate this by the following arguments and data: The total health care costs of cancer per person varies widely within EU countries not only concerning outpatient and primary care, but also inpatient care and particularly drug expenditures. Cancer drug-related health care costs, thus differ between less than €10. -per person up to over €50. -per person. This divergence has been described previously and put into context with cancer outcomes (i.e. as well as cancer-associated mortality (2). Therefore, the European Society for Medical Oncology decided to create a magnitude of clinical benefit scale (ESMO-MCBS) in order to promote high quality, rational and affordable cancer care wanting to highlight treatments which bring substantial improvement in the duration of survival and the quality of life of cancer patients (3). It was intended that the scale was used for accelerated reimbursement evaluation. Factors taken into account for the ESMO-MCBS were particularly overall survival and/or progression-free survival as assessed by hazard ratios, quality of life, toxicity of the compound in question and the diagnosis of the group of patients. Costs were not excluded in view of their significant heterogeneity across Europe. While generating two different scales for the curative versus the non-curative setting, a couple of rules were followed regarding the performed analyses: In the priority was a strong level of evidence from large phase III studies with a careful analysis of each control arm and the identification of endpoints. For the required HR, the lower limit of the 95% CI was used to take into account the variability of the estimate. Before being published, the scale and its outcomes were broadly tested and evaluated in and by various institutions. The first full-length field testing (FT-MCBS) of the ESMO-MCBS was published recently (4) in which the use of non-small cell lung cancer was included.

The ESMO-MCBS of the immune checkpoint inhibitor Nivolumab, the FT-MCBS generated the highest grade (i.e. “5”) for squamous NSCLC according to data generated in the Checkmate 017-Trial whereas a grade “4” was given for non-squamous NSCLC, as assessed in the Checkmate 057-Trial. Thus, the immune checkpoint inhibitor Nivolumab has acquired the highest or almost highest degree in the magnitude of clinical benefit, as assessed by the FT-MCBS scale. Soon after market introduction, concerns about the financial toxic dose of immune checkpoint inhibitors emerged leading to the rejection of Nivolumab in the second-line-treatment of NSCLC, whereas - in contrast - the Scottish authorities decided to include Nivolumab into their reimbursement strategies. Very recent analyses on this very topic showed that Nivolumab was not cost effective versus Docetaxel in the second-line-treatment of NSCLC based upon data generated in Checkmate 057-Trial. However, cost-effectiveness studies could be performed by including and stratifying patients according to PD-L1 testing and the use of Nivolumab in PD-L1 overexpressing tumors on one side or – in statistical models - the reduction of drug costs on the other. Either of these strategies would improve the cost effectiveness of Nivolumab (5, 6) Scientifically, however, the doubt remains to linger whether PD-L1 would be an optimal biomarker resulting in appropriate decision making for the choice of compound optimally suitable for the treatment of NSCLC. While unjustly excluding patients who might have benefitted due to other factors from treatment: Thus, it is well known that certain somatic mutations occur more frequently in very special tumors than in others (7). Along this line, a biomarker (nECI) corresponds well with higher non-synonymous mutation burden in the Checkmate 063-Trial population (8). Therefore, it seems correct to conclude that we still have a long way to go to fully understand biomarkers predictive for the outcome of an optimal treatment of NSCLC with immune checkpoint inhibitors. Accordingly, appropriate analyses necessary for biomarker identification might translate into cost effectiveness. Such analyses might result in a primarily increased diagnostic cost, but lead to an ameliorated patient selection and, thus, ameliorated cost effectiveness in the appropriate use of immune checkpoint inhibitor treatment in NSCLC. In the meantime, the scientific community remains fascinated by the insights and results which are generated by the use of these compounds in a variety of diseases including NSCLC. Reference: 1. Jezdejewski M. et al., The Oncologist 20: 28, 2015; 2. Ades F. et al., Ann. Oncol. 24: 2897, 2013; 3. N.I. Cherry et al., Ann. Oncol. 26: 1547, 2015; 4. B. Kiesewetter et al., ESMO Open 1: e000066, 2016; 5. K. Matter-Walstra et al., J. Thoracic Oncol., 2016. ePublished: http://dx.doi.org/10.1016/j.jtho.2016.05.032, 6. P. N. Aguiar et al., J. Clin. Oncol. 34, abstr. 9033, 2016; 7. L. B. Alexandrov et al., Nature 22: 415; 2013; 8. N. A. Rizvi et al., Science, 2015, ePub: pii.a9348

Keywords: Immune Checkpoint Inhibitors, Cost-Effectiveness, Clinical Benefit, ESMO

SESSION SC23: THE IMPORTANCE OF CO-OPERATIVE GROUPS TUESDAY, DECEMBER 6, 2016 - 16:00-17:30

SC23.01 COOPERATIVE GROUPS IN LATIN AMERICA Clarissa Mathias Medical Oncology, NOB, Salvador/Brazil

More than 100 million people in Latin America will be ≥ 60 years of age by
Abstracts

2020. Age, smoke exposure and infectious causes of cancer (HPV, Hepatitis B, and H. pylori) will continue to drive the burden of cancer in the region. Cancer mortality rates in Latin America are approximately twice those of the United States (1). Until not so long ago, drug development and cancer clinical research were conducted almost exclusively in wealthy developed regions of the world. However, over the last 2 or 3 decades, clinical trials have been progressively incorporated in a challenging globalization process. As such, the conduct of trials in a global scale represents a major aspect to be taken into account when analyzing the development of the research in clinical trials, as well as multinational and multi-institutional research collaboration, represents a scenario that requires permanent and concentrated efforts by all involved if we are to achieve the fundamental objective of generating the appropriate answers to the health problems we face around the world (2). Up to this point, the conduct of trials in Latin America has had an increasing participation from research groups in the region. In large registered phase III studies, 40% are conducted in the United States, 43% in Western Europe, and 17% in Latin America (5). Involvement of investigators from developing countries in the planning phases of the trials is essential as they may provide valuable contribution while being exposed to an experience that will have long lasting impacts in the future development of science, with more than just scientific contributions. Research results are often conveyed to the worldwide medical community through scientific publications. In order to complete the trials and publish, investigators must overcome many financial, institutional, and cultural barriers. Achieving appropriate levels of research quality and protection of study subjects. Some decades ago, the development of global clinical research could have been considered a dream; it is now a pressing need that should be considered unavoidable in the future (3). Some references: 1) Gosh, P; Lee, B; Bowinovic-Chevic, T et al. Planning Cancer Control in Latin America and the Caribbean. Lancet Oncol 2013; 14: 391–436 2 Barrios, C, Werutzky, G and Martinez-Mesa, J. The Global Conduct of Cancer Clinical Trials: Challenges and Opportunities. ASCO Educational Book, e33–e139, 2015 3 Drain PK, Robine M, Holmes KK, et al. Trail watch: an analysis of the global migration of clinical trials. Nat Rev Drug Discov. 2014;13:166-167 4 Thiers FA, Sinisgalli AJ, Ernst R. Trends in the globalization of clinical trials. Nature Reviews Drug Discovery. 2008;7:134-5. 5 www.clinicaltrials.gov 6 Katkin KI. The Landscape for pharmaceutical innovation: drivers of cost-effective clinical research. Pharm Outsourcing. 2010;2010: 3605. 7 Roflo C, Cagvelic C, Baret B et al. Cancer clinical research in Latin America: current situation and opportunities. Expert opinion from the first ESMO workshop on clinical trials, Lima, 2015. ESMO Open 2016;1 8 Smith WT. FDA requires foreign clinical studies be in accordance with Good Clinical Practices, FDA’s foreign clinical trials regulations. FDA requires foreign clinical trials be in accordance with Good Clinical Practices, FDA’s foreign clinical trials regulations.

Keywords: Cooperative Groups, Latin America, research

SC23.03 HOW COULD HIGH-VOLUME CENTERS IN DEVELOPING COUNTRIES ACCESS COOPERATIVE GROUP TRIALS?

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Lung cancer has the second highest absolute incidence globally as well as in developing countries and ranks fourth in developed countries. It is the most common cause of cancer death by absolute cases globally as well as in developing and developed regions. The economic burden of lung cancer is highest relative to other cancers in the European Union, research is at the core of achieving improved outcomes from cancer, but is limited by specific epidemiology of the disease, understanding the pathogenesis of disease, identifying new targets for therapeutic agents, or directing policy to achieve affordable and equitable outcomes. Cancer research are one of the most intensely active domains of science, with more than 7 billion dollars annually. A critical part of the health research portfolio is the testing of interventions through randomized controlled trials. Trials can range from highly controlled explanatory trials through to pragmatic trials of new health technologies and models of service delivery. Recruitment problems also have practical and financial impacts, as they can delay completion of research or reduce its timely impact on patient health and wellbeing. Achieving appropriate levels of patient and professional participation has been a significant obstacle to evidence-based practice. Published data show that the minority of trials recruit successfully, either in terms of reaching their planned sample size, or determining the planned sample in the expected recruitment window. Despite all the difficulties, clinical trials have become increasingly globalized due to the inclusion of more non-traditional locations, especially those in central and eastern Europe, Latin America, and Asia. The increased globalization of clinical research has arisen for several reasons, but primarily due to the need for faster and more economically efficient studies. Moves towards standardizing and harmonizing clinical research practices have facilitated the rise of globalized clinical research. However, the expansion of multinational clinical research peaked in 2009, which could reflect that the large-scale expansion of multinational clinical research effort has reached its global capacity. When the distribution of multinational clinical trials is examined after being stratified according to the condition or disease, lung cancer is not among the five most frequently studied conditions apart from Asia. The results of a bibliometric analysis of global research on lung cancer between 2004-2013 in the 4 leading countries in cancer research showed that despite a doubling of the volume of lung cancer research worldwide between 2004 and 2013, it still only accounts for a small proportion of the overall oncology research publication output (5.6%). In fact, the relative commitment (RC) to lung cancer research compared with that to total oncology research output has fallen in most countries during this period, including in the 33 countries with the exception of the China. Turkey, Poland, Canada, Greece, and the United States, despite having the highest country-specific burden of lung cancer, have all seen a decrease in their RC to lung cancer research. Research from Norway, Austria, Switzerland, Belgium, and Sweden had the highest proportion of international contributors. By comparison, relative to their research output, the East Asian countries (Taiwan, India, the Republic of Korea, and Japan) and Turkey had the least amount of international collaboration. With regard to multinational studies, only 1.2% of articles had collaborators from five or more countries and 0.3% from 10 or more countries. The aim of co-operative groups in oncology is to perform multi-center clinical trials to achieve standardizing and harmonizing clinical research practices. Research results are often conveyed to the worldwide medical community through scientific publications. In order to complete the trials within the period specified, it is obvious the need of the qualified and high-quality research and protection of study subjects. Some decades ago, the development of global clinical research could have been considered a dream; it is now a pressing need that should be considered unavoidable in the future (3). Related references: 1) Gosh, P; Lee, B; Bowinovic-Chevic, T et al. 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FDA requires foreign clinical studies be in accordance with good clinical practices to better protect human subjects. ABA Health eSource. 2008;5-3.
volume cancer centers. The barriers to participation of high-volume hospitals in the cooperative group trials should be determined and eliminated. Since the 1970s, centers for thoracic diseases that emerged from former tuberculosis hospitals, particularly in Europe, have focused on the diagnosis and treatment of patients with lung cancer. Traditionally, these centers were staffed by pulmonologists and thoracic surgeons, but now include an extended range of health care workers including the disciplines of radiation oncology, medical oncology, palliative care and rehabilitation medicine. These high-volume cancer centers treat many patients with problems affecting patients with lung cancer. In 2010, the hospitals with a median 400 new patients per year were in Albania, Belarus, Bulgaria, the Czech Republic, Poland, Romania and Slovenia. The hospitals with more than 1000 new patients with lung cancer per year were in Poland, Bulgaria, Croatia, Turkey. We have to foster the cooperative study groups of lung cancer to provide collaboration between study group and these hospitals. High-volume hospitals should be identified and hospital-based representatives should be determined. Supreme organisations as European Thoracic Oncology Platform providing collaboration among study groups and hospitals, should be able to invite the high-volume hospitals with site evaluation. These high-volume centers have to review whether adequately equipped and set up not for participation in research projects and clinical trials. References 1- Gaglia M. An Official American Thoracic Society/European Respiratory Society Statement: The role of the pulmonologist in the diagnosis and management of lung cancer. Am J Respir Crit Care Med 2013; 188(4): 503-7. 2- Blum T.G. The European initiative for quality management in lung cancer care. Eur Respir J, 2014, 43: 1254-77-3; Loddenkemper R, 100 years DGP-100 years of pneumology in Germany. Pneumologie 2010, 64:7-17. 4- Richter TA. Clinical research: A globalized network. PLoS ONE 2014, 9(2):1-13:2 - Aggarwal A. The state of lung cancer research: A global analysis. J Thorac Oncol 2016; 11(7): 1040-50.

Keywords: clinical trial, lung cancer, study groups

SC23.04 COOPERATIVE GROUPS IN CHINA: THE CSCO EXPERIENCE
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In order to keep up with the rapid development of world cancer treatment exploring, Chinese clinical oncology professionals, relevant enterprises and public institutions voluntarily constituted a non-profit professional academic group which is known as The Chinese Society of Clinical Oncology (CSCO) in April 1997. The CSCO organization and cooperative relationship to international collaboration such as establishing reciprocal memberships with American Society of Clinical Oncology (ASCO), European Society for Medical Oncology (ESMO), Clinical Oncological Society of Australia (COSA) and participating represent of professional organization of Asia Society of Clinical Oncology (ASCOS), but also committed to Chinese Oncology development. The CSCO annual meeting delivered the latest advancements and research fruit from home and abroad which offered a great academic exchange platform for vast amount of Chinese oncologists. CSCO also organize experts to make tumor diagnosis and treatment standardized globalization. Up to date, CSCO has launched dozens of guidelines regarding many major cancers in China, including non-small cell lung cancer, colorectal cancer and hepatocellular carcinoma. The newly made guideline about non-small cell lung cancer has fully considered Chinese special situation, not only disease characteristics, but also social economic factors, which made a good example of better suiting Chinese oncologists and patients. Other than this, CSCO developed multi-center clinical researches which offered solid evidence for Chinese cancer patients and made contribution to world cancer diagnosis and treatment. Most of clinical researches were carried out by Study Group majored in different cancers, such as Chinese Breast Cancer Study Group (CBCSG) and Chinese Gastrointestinal Oncology Group (CGGO). The CSCO also keeps an open mind and follows the trend of hot spot, such as building expert committee on cancer biomarkers and precise practice of thoracic tumor, promoting standardization, modernization and internationalization of clinical and research work in thoracic tumor area and finally improving the level of diagnosis and treatment of chest tumors in China as well as international status. CTONG has actually made massive efforts and achieved great success. Up to date, CTONG has 31 members from 15 provinces and municipality cities and has successfully performed 47 clinical trials in China. Half of these clinical trials established China lung cancer treatment modalities. Take CTONG 0802 study (OPTIMAL) for example, the multicenter open-label randomized phase II study compared erlotinib with combination of gemcitabine and cisplatin in first-line treatment of patients with EGFR mutation-positive NSCLC. Median progression-free survival was significantly longer in erlotinib-treated patients than in those on chemotherapy (13.1 vs. 5.6 months; hazard ratio 0.15; 95% CI 0.10-0.26; p<0.0001). Chemotherapy was associated with more grade 3 or 4 toxic effects than was erlotinib (including neutropenia in 30 [42%] of 72 patients and thrombocytopenia in 29 [40%] of 72 patients with either event on erlotinib), which suggested that erlotinib is important for first-line treatment of patients with advanced EGFR mutation-positive NSCLC. The results of CTONG0802 was orally presented on ESMO2010, WCLC 2011, discussed on ASCO 2011 and published on Lancet Oncol. CTONG 0901 study compared erlotinib with gefitinib in patients with EGFR mutation positive stage IIIb/IV NSCLC and found no PFS or OS difference between these two regimens which offered solid evidence for clinical choice. CTONG also paid attention to first-line maintenance therapy, second-line treatment, Another well-known study of CTONG is FASTACT-II (CTONG0902) proved that erlotinib maintenance therapy after first-line gemcitabine combined with cisplatin improves overall survival of stage IIIB/IV NSCLC patients. CTONG 0806 study suggested improved OS in PFS and an improved OS trend with pemetrexed compared with gefitinib as second-line setting treatment of EGFR wild-type advanced non-squamous NSCLC. There were also many studies for first-line treatment, second-line treatment, brain metastasis and peri-operative treatments and achieved meaningful results in these fields. Additionally, CTONG has initiated the very first real-world study in China targeting first-line treatment pattern of advanced non-squamous NSCLC patients, the study conducted between scientific achievements and clinical practice in China and set a great beginning of caring for patients’ actual profits. The currently ongoing reform for new drug approval of CFDA provides great chances for the development of clinical trials in China and domestic drug innovation such as icotinib and apitinib. CTONG and other study groups also face many challenges. CTCG’s success and experience of CSCO study groups, is expected to make more contributions to china lung cancer treatment. Hopefully, CSCO achievements will finally benefit more Chinese cancer patients and make more contribution to world cancer control. Reference: 1. Zhou C, Wu YL, Chen G, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. Lancet Oncol. 2011;12(8):735-742. 2. Yang JJ, Zhou Q, Yan HH, et al. A Randomized Controlled Trial of Erlotinib versus Gefitinib in Advanced Non-Small-Cell Lung Cancer Harboring EGFR Mutations (CTONG0903). J Thorac Oncol 2015; 10(11): 1722-8. 3. 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Keywords: Chinese Thoracic Oncology Group (CTONG), Cooperative Groups, Chinese Society of Clinical Oncology (CSCO)
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stage IA (Fig. 1). Preoperative PET-CT and thin-section CT findings together can provide adenocarcinomas (MIA) of the lung that show solid opacities on HRCT, the dominant and solid-dominant lesions were 51.2% and 75.6%, respectively (nodules, especially GGO-dominant nodules, is challenging. The diagnostic bronchoscopy, or surgery is used for obtaining specimens for diagnosis by HRCT can be difficult, and the combination of HRCT and PET-CT does not allow evaluation of lymph nodes for metastatic disease. Especially wedge resection, dose not allow evaluation of lymph nodes for metastatic disease. Since invasive biopsy is not without risk, a histopathological diagnosis should be delayed to nonsurgical candidates. For cases with high likelihood of lung cancer, a surgical biopsy followed by lung resection might be warranted. Although surgery might be performed on patients with benign nodules, it does provide the definitive diagnosis. If surgery is performed after careful preoperative assessment, the surgical mortality is very low, and the surgical risk may be acceptable. Treatment: While lobectomy is the standard procedure for lung cancers, sublobar resection, meaning segmentectomy or wedge resection, might be justified for patients with noninvasive small lung cancers. However, to date, which procedure, sublobar resection or lobectomy, provides a better outcome remains unclear in these cases, since prospective randomized control trials are ongoing (JCOG0802/JWOG4607L and CALGB140503). One of the concerns in sublobar resection is recurrence at the surgical margin (Fig. 2). Recurrence at the surgical margin might be accounted for by tumor cells spreading via air spaces. Accurate intraoperative cytology and adequate surgical margins have been reported to be important for preventing recurrence at the surgical margin. Another concern is lymph node metastasis. In a prospective radiological study for clinical stage IA lung cancer, 47 of 545 (8.6%) patients had lymph node metastases. Sublobar resection, especially wedge resection, does not allow evaluation of lymph nodes for metastatic disease. Therefore, lymph node metastasis plays an important role in discriminating the biological behaviors of pulmonary nodules. The definitive diagnosis by HRCT can be difficult, and the combination of HRCT and PET-CT might be beneficial. Randomized control trials should clarify the role of sublobar resection in treating patients with noninvasive lung cancer. Figure 1.

Radiological group & Invasive lung cancer

<table>
<thead>
<tr>
<th>Radiological group</th>
<th>Invasive lung cancer (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SUV index ≥ 1.0 and solid</td>
<td>37.9</td>
</tr>
<tr>
<td>SUV index &lt; 1.0 and solid</td>
<td>24.2</td>
</tr>
<tr>
<td>SUV index ≥ 1.0 and non-solid</td>
<td>41.3</td>
</tr>
<tr>
<td>SUV index &lt; 1.0 and non-solid</td>
<td>23</td>
</tr>
<tr>
<td>SUV index ≥ 1.0 and solid</td>
<td>58</td>
</tr>
<tr>
<td>SUV index &lt; 1.0 and non-solid</td>
<td>41</td>
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<tr>
<td>SUV index ≥ 1.0 and solid</td>
<td>58</td>
</tr>
<tr>
<td>SUV index &lt; 1.0 and non-solid</td>
<td>41</td>
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</tbody>
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SUV index: The corrected SUV was calculated as the ratio of tumor SUVmax to liver SUVmean. Invasive lung cancer: Invasive lung cancer was defined by lymph node metastasis, lymphovascular invasion or pleural invasion.

References

Keywords: pulmonary nodules, computed tomography, sublobar resection, lung cancer

SC24: MANAGEMENT OF INDETERMINATE PULMONARY NODULES
WEDNESDAY, DECEMBER 7, 2016 - 11:00-12:30

SC24.02 RADIOLOGICAL TECHNIQUES FOR THE EVALUATION OF PULMONARY NODULES
Reginald Munden
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Radiologic Techniques for the Evaluation of Pulmonary Nodules The incidental detection of pulmonary nodules has increased with improved CT technology and thin section imaging techniques. Adding to this increased detection of nodules is the heightened interest in the purposeful search for nodules such as in oncology patients and lung cancer screening programs. The management of CT detected nodules is a subject of much debate and dependent upon the clinical setting. For instance, in a lung cancer screening setting, there has been a large volume of investigation of solid, semi-solid and ground glass nodules that is the foundation of management recommendations such as LungRads®. In patients with a known malignancy, there is minimal literature on management recommendations and thus more influenced by pulmonary metastatic potential of the malignancy and clinician experience. Finally incidentally detected nodule management is greatly influenced by cancer risk factors and nodule texture; for these situations, the Fleischner criteria have been the most widely used and accepted management guidelines. The radiologic evaluation of nodules most often utilizes conventional imaging techniques of chest radiographs, computed tomography (CT), PET/CT. Occasionally MRI and ultrasound may be employed. Most recent changes involve risk stratification, computer software applications to enhance nodule analysis such as nodule enhancement patterns, volumetric computations, and texture analysis. Future directions include incorporation of genomics into imaging as well as radiomic analysis and machine learning.

Keywords: Radiomics, Incidental, nodules, CT

SESSION SC26: ANGIOGENESIS INHIBITION: ADVANCES & PERSPECTIVES
WEDNESDAY, DECEMBER 7, 2016 - 11:00-12:30

SC26.02 ANGIOGENESIS INHIBITION IN LUNG CANCER: RECENT ADVANCES AND PERSPECTIVES
Michael Boyer
Department of Medical Oncology, Chris O’Brien Lifehouse, Camperdown (NSW)/Australia

Angiogenesis is an important process in the development and progression of tumors. Across a range of tumour types markers of angiogenesis, such as elevated VEGF levels or increased micro vessel density, have been shown to be associated with poorer patient outcomes. The recognition that VEGF mediated signal transduction is a key driver of angiogenesis has led to the development of a range of anti-angiogenic approaches targeting this biological process. These approaches have included monoclonal antibodies (bevacizumab, ramucirumab), decoy receptors (aflibercept), and receptor tyrosine kinase inhibitors (nintedanib, sorafenib, sunitinib, motesanib, Vandetanib, cediranib, pazopanib), all of which have been evaluated in lung cancer. Despite this volume of clinical research, only three of these agents (bevacizumab, ramucirumab, cediranib) have been evaluated in lung cancer. Across a range of tumour types markers of angiogenesis, such as elevated VEGF levels or increased micro vessel density, have been shown to be associated with poorer patient outcomes.

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SC26: ANGIOGENESIS INHIBITION: ADVANCES & PERSPECTIVES
WEDNESDAY, DECEMBER 7, 2016 - 11:00-12:30

SC26.03 PREDICTIVE BIOMARKERS FOR ANGIOGENESIS INHIBITORS: AN UPDATE

HR (0.68, 95% CI 0.50 – 0.93; p = 0.015), with median OS increasing from 17.7 to 24.3 months. Bevacizumab has also been evaluated in the second line setting in combination with etoribulin (in patients unselected for EGFR mutations), without a significant impact on overall survival. Based on these results, Ramucirumab is a monoclonal antibody directed against the VEGFR2 receptor. It has been evaluated in a randomised trial in the second line setting. Patients were randomised to receive treatment with docetaxel or with or without ramucirumab7. Treatment was continued till progression, with monotherapy ramucirumab continued till toxicity developed or docetaxel (and subsequent). The primary endpoint of the study was overall survival, and the results indicated an improvement in overall survival for patients receiving ramucirumab (HR 0.86, 95% CI 0.75 – 0.98; p = 0.023), with median survival increasing from 9.1 to 10.5 months. By contrast to the various studies of bevacizumab, this study enrolled patients with non-squamous tumours, as well as those with non-squamous tumours, with the magnitude of benefit being similar in both histologic types. Addition of ramucirumab resulted in an increase in toxicity, with more hypertension, bleeding, and febrile neutropenia. However the rate of serious adverse events and of deaths due to adverse events were similar between the two arms. The results from this study led to the approval of ramucirumab for patients with previously treated in NSCLC in some parts of the world, including the USA and Europe. However, subsequently, the results of trials of immune checkpoint inhibitors in the same patient population has resulted in many of these patients not receiving bevacizumab due to the risks of toxicity and feasibility of this agent. The addition of a tyrosine kinase inhibitor to chemotherapy has been evaluated extensively in patients with advanced NSCLC in both the first and second line settings. The results of these trials have been disappointing, with little if any improvement over survival achieved by the combination of chemotherapy and targeted therapy. These trials, however, did show some improvement in progression free survival. Only one of these agents, nintedanib, is approved (in Europe) for the treatment of patients with NSCLC. This is based on the results of the LUME-1 study, which compared treatment with docetaxel alone with docetaxel plus nintedanib in patients with previously treated NSCLC. In this study, progression free survival (the primary endpoint) was longer with the addition of nintedanib (3.4 vs 2.7 months, HR 0.79, 95% CI 0.68 – 0.92; p = 0.0019). Although there was no difference in overall survival in the whole study population, in the predefined subset of patients with adenocarcinoma and progression within 9 months of initial therapy median overall survival increased from 7.9 to 10.3 months (HR 0.75, 95% CI 0.60 – 0.92; p = 0.007). Similar, though less extreme results occurred in all patients with adenocarcinoma. There was no effect on survival of patients with squamous histology. The combination resulted in an increase in the rate of adverse events, predominantly diarrhoea, liver function abnormalities and vomiting, no biomarker differences were identified, which allows the selection of patients for treatment with bevacizumab. As a consequence, patient selection (for bevacizumab) is based on the avoidance of toxicity, by excluding groups of patients known to be at higher risk (e.g. those with squamous cell histology, or a history of haemoptysis). Furthermore the inability to identify those patients who most likely to benefit, along with the relatively small improvements in survival means that from an economic viewpoint, the cost per life year gained is high. This has resulted in antiangiogicnnot being widely used in some countries. References 1. Paci et al. Carboplatin plus paclitaxel alone or with bevacizumab for non-small-cell lung cancer. Sandler et al. N Engl J Med 2006; 355: 2542 – 2550 2. Phase III trial of cisplatin plus gemcitabine with either placebo or bevacizumab as front-line therapy for non-squamous non-small-cell lung cancer: AVAiL. Reck et al. J Clin Oncol 2009; 27: 1227 – 1234 3. Systematic review and meta-analysis of randomised, phase II/III trials adding bevacizumab to platinum based chemotherapy as front-line treatment in patients with advanced non-small cell lung cancer. Soria et al. Ann Oncol 2013; 24: 20 – 30 4. BEYOND: A randomized, double-blind, placebo-controlled, multicentre phase III study of first-line carboplatin/paclitaxel plus bevacizumab or placebo in Chinese patients with advanced or recurrent non-squamous non-cell lung cancer. Zhou et al. J Clin Oncol 2015; 33: 2197 – 2204 5. Efficacy of bevacizumab plus erlotinib versus erlotinib alone in advanced non-small-cell lung cancer after failure of standard first-line chemotherapy (BEA): a double-blind placebo-controlled phase 3 trial. Herbst et al. Lancet 2011; 377: 1846 – 1854 6. Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre double-blind randomised phase 3 trial. Lancet 2014; 384: 665 – 673 7. Docetaxel plus nintedanib versus docetaxel plus placebo in patients with previously treated non-small-cell lung cancer (LUME-1): a phase 3 double blind, randomised controlled trial. Reck et al. Lancet Oncol 2014; 15: 143-155

Keywords: angiogenesis

SC26.03 PREDICTIVE BIOMARKERS FOR ANGIOGENESIS INHIBITORS: AN UPDATE
WEDNESDAY, DECEMBER 7, 2016 - 11:00-12:30
S70

Lung cancer is still the leading cause of cancer-related death in both men and women with 80% to 85% of cases being non-small-cell lung cancer (NSCLC). The past fifteen years have brought significant breakthroughs in the understanding of the molecular biology of lung cancer. Signal transduction pathways and genetic driver mutations that are vital for tumour growth have been identified and can be effectively targeted by novel pharmacologic agents, resulting in significantly improved survival of patients with lung cancer. Parallel to the progress in lung cancer treatment, imaging techniques aiming at improving diagnosis, staging, response evaluation, and detection of tumour recurrence have also considerably advanced in recent years. However, standard morphologic computed tomography (CT) and magnetic resonance imaging (MRI) as well as fluor-18-fluorodeoxyglucose (18F-FDG) positron emission tomography CT (PET-CT) are still the currently most frequently utilized imaging modalities in clinical practice and most clinical trials. Novel state-of-the-art functional imaging techniques such as dual-energy computed tomography (DECT), dynamic contrast enhanced CT (DCE-CT), diffusion weighted MRI (DW-MRI), perfusion MRI, and PET-CT with more specific tracers that visualize angiogenesis, tumour oxygenation or tumour cell proliferation have not yet been widely implemented, neither in clinical practice nor in phase I–III clinical trials. In this context, Nishino et al.1 published an analysis of the available tumour response assessment in the era of molecular treatment in oncology. The authors showed that the concept of personalized medicine with regard to cancer treatment has been well applied in therapeutic decision-making and patient management in clinical oncology. With regard to imaging techniques, however, it was criticized that the developments in tumour response assessment that should parallel the advances in cancer treatment are not sufficient to produce state-of-the-art functional information that directly reflect treatment targets. Functional information on tumour response is highly required because there is growing evidence that the current objective criteria with respect to progression or response do not reliably indicate treatment failure and do not adequately capture disease biology. Molecular-targeted therapies and novel immunotherapies induce effects that differ from those induced by classic cytotoxic treatment including vascular endothelial growth factor (anti-VEGF) antibody bevacizumab, factors like rapid progressive diseases or tumors refractory to conventional chemotherapy could be associated with improved outcomes of angiogenesis inhibitors. Preplanned as well as exploratory analyses did show pronounced efficacy for the combination of antiangiogenic agents like nintedanib, ramucirumab and bevacizumab compared to chemotherapy alone supporting the hypothesis that fast progressing tumors are more dependent on neoangiogenesis. The translational exploration of these clinical findings is on the way in several programs and trials. The understanding of this correlation will be important for the optimal placement of antiangiogenic agents e.g. in the combination with immunotherapies.

Keywords:
Angiogenesis, Biomarker, NSCLC, rapid progressive tumors

SC26.04 NOVEL IMAGING TECHNIQUE
Stefan Schönberg
Institute of Clinical Radiology and Nuclear Medicine, University Medical Center Mannheim, Medical Faculty Mannheim, Heidelberg University, Mannheim/Germany

Lung cancer is still the leading cause of cancer-related death in both men and women with 80% to 85% of cases being non-small-cell lung cancer (NSCLC). The past fifteen years have brought significant breakthroughs in the understanding of the molecular biology of lung cancer. Signalling pathways and genetic driver mutations that are vital for tumour growth have been identified and can be effectively targeted by novel pharmacologic

SESSION SC27: PS5 AND KRAS MUTATIONS IN NSCLC
WEDNESDAY, DECEMBER 7, 2016 - 11:00-12:30

SC27.02 BIOLOGY OF KRAS MUTATIONS
İzzet Timar

Journal of Thoracic Oncology • Volume 12 Issue S1 January 2017
Molecular classification of lung cancer revealed that the most frequently mutated oncogene in lung cancer is the KRAS due to smoking and this molecular subclass is exclusively occur in the adenocarcinoma histologic variant and rarely in large cell variant. It also can be detected in the mixed histologic variants like the adenosquamous subtype. The incidence of KRAS mutation in lung adenocarcinoma is 30% based on exon2 testing. (1) However, it is known that also in colorectal cancer, a colorectal cancer panel was used to help to clearly define a large set of adenocarcinoma patents where further molecular analysis is not necessary. Analysis of two large patient cohort of lung adenocarcinoma and colorectal cancer (500 pt each) revealed that the allelic variations are highly similar in mutant KRAS exon2 in this two cancer types. The TGT (G-C) transversion in codon 12 was proved to be lung cancer specific while the GAC (G-D) codon 13 alteration was colorectal cancer specific. Since the KRAS mutation in lung cancer is considered to be smoking related, this highly similar allelic profile in colorectal cancer can be the molecular signature of smoking in this cancer type. Analysis of KRAS exon 2 aminoacid conversions of smoking status revealed that in non-smokers mutation is rare and if it occurs it is most frequently G12V unlike in smokers where G12C is the predominant. G12V-type patients may respond better to conventional chemotherapy (2). RAS mutant lung cancer patients are resistant to EGFR TKI inhibitors (3). EGFR protein expression is highly similar in KRAS mutant and wild lung adenocarcinoma but interesting the phosphorylated-EGFR is overexpressed in KRAS mutant tumors even overcoming EGFR mutated ones suggesting an aberrant RAS-driven signaling. (3) KRAS mutation in lung cancer is a poor prognostic factor. Analysis of the organ metastatic pattern of KRAS mutant lung adenocarcinoma revealed that brain and bone metastatic potential of KRAS wild type are similar. This evidence suggests that while KRAS may tend to prefer pleural dissemination and liver. On the other hand, KRAS mutant lung adenocarcinoma is less likely give rise adrenal- or lung metastasis, a clearly indication a different biology as compared to KRASwt cancers. It is an important issue today the maintenance of the molecular profiles of metastases obtained from the primary and the metastatic site may be sensitive in patients where surgical removal of the primary is impossible (a significant proportion of lung cancers) while can be more significant where only metastases are present in the patients. Analysis of the literature data indicates that the survival benefit rate of RAS mutant lung cancer is low (below 10%), in case of visceral metastases increases to 14-24% range while is was reported to be the highest in bone metastasis (3). Lung cancer is reported to be a clonally heterogenous cancer and these alterations are most probably due to clonal variations during metastatic dissemination. The advent of liquid biopsy technology monitoring of this process is now feasible using circulating DNA. A major issue clinically today is the development of resistance to target therapies. Both lung adenocarcinoma and colorectal cancer is treated by EGFR targeted therapies where the molecular mechanisms of acquired resistance are now reported. It is interesting that in colorectal cancer panitumumab, the main causative agent to anti-EGFR antibody therapy is the emergence of RAS mutated clones in progressing tumours which were in majority in the primary. Although RAS mutation is frequently equal in lung adenocarcinoma, EGFR-TKI resistance is most frequently due to EGFR T790M or HER2 amplification but no report on resistance of RAS mutated clones. (4) In case of ALK mutant lung adenocarcinoma resistance to ALK inhibitors is mainly due to novel mutations in ALK. In a small proportion of cases KRAS amplification or NRAS mutation can be detected which suggest that in ALK-translocated lung cancer no minor RAS mutant clones are present in the tumors. (5) Check point inhibitor therapy is a new modality of lung cancer management targeting CTLA4, PD1 or PD-L1 as targets on immune cells or cancer cells (PD-L1). Although two drugs are registered in NSCLC, the significance of RAS mutations in this new modality is not known yet. In case of Nivolumab it is known that smokers are responding poorly to anti-PD1 therapy as compared to nonsmokers suggesting that KRAS mutant tumors might be a better target but direct subgroup analysis is lacking. In case of Pembrolizumab even such an indirect data are missing therefore the question cannot be answered yet. The fact that EGFR mutant tumors are tend to respond less to anti-PD1 therapy suggest that beside PD-L1, molecular classification may also be necessary for selecting patients for immunotherapy. (6) References 1.Trimaj: The clinical relevance of KRAS gene mutation in non-small-cell lung cancer. Curr Oncol 26: 138-144, 2014 2. Cserepes M, Ostoros Gy, Lohinai Z, Rásé E, Barbai T, Trimaj, Rozsás A, Molváj J, Kovalszky J, Fabian K, Gyulai M, Ghanim B, László V, Klikovics B, Dömösi B, Gajic J: KRAS mutations in advanced lung adenocarcinoma: A retrospective study of patients treated with platinum-based chemotherapy. Eur J Cancer 50: 1819-1828, 2014 3. Molváj J, Barbai T, Bogos K, Pirkus V, Fillingr J, Popper HH: A novel function of a protein post-translational modification by histologic and molecular subtypes in lung adenocarcinoma. Diagn Mol Pathol 22: 204-209, 2013 4. Belich SA, Tseng LH, Gmiadek T et. al. Heterogeneity of resistance mutations detectable by next-generation sequencing in TKI-treated lung adenocarcinoma. Oncotarget 2016 (in press) 5. Daggo-Jack I, Show AT. Citotinib resistance: implications for therapeutic strategies. Ann Oncol 23:ii42-ii50, 2016 6. El-Osta H, Shahid K, Mills GM, Peddi P. Immune checkpoint inhibitors: the new frontier in non-small-cell lung cancer. Oncotarget 9:5101-5106, 2016 Keywords: KRAS, lung adenocarcinoma, Prognosis, mutational profile SC27: PD-L1 EXPRESSION IN PRIMARY LUNG CANCER: PHOTODYNAMIC THERAPY AS AN ADJUVANT 1. Introduction Photodynamic therapy (PDT) is a modality that has been studied in the treatment of non-small cell lung cancer (NSCLC). The mechanism of action of PDT involves the delivery of a photosensitizer to the tissue, after which laser light of a specific wavelength is delivered, resulting in the formation of singlet oxygen and other reactive oxygen species, which lead to cell death. The efficacy of PDT is known to be influenced by several factors, including the presence of specific mutations in the KRAS gene. In this study, we aimed to investigate the expression of PD-L1 in primary lung cancer specimens and its correlation with KRAS mutations. 2. Methods We retrospectively reviewed the medical records of 150 patients with NSCLC who underwent surgical resection and adjuvant therapy at our institution. The specimens were analyzed for PD-L1 expression using immunohistochemistry (IHC) and for KRAS mutations using targeted sequencing. The correlation between PD-L1 expression and KRAS mutations was assessed using the chi-square test. 3. Results A total of 150 patients were included in the study, with 100 patients having adenocarcinoma and 50 having squamous cell carcinoma. The expression of PD-L1 was positive in 60% of cases (90/150). KRAS mutations were identified in 30% of cases (45/150). There was a statistically significant correlation between PD-L1 expression and KRAS mutations (p < 0.05). PD-L1 expression was higher in KRAS mutant tumors compared to KRAS wild-type tumors. 4. Discussion Our findings suggest that PD-L1 expression may be a useful biomarker for the identification of KRAS mutant tumors, which may benefit from adjuvant PDT. Further research is needed to confirm these findings and to evaluate the clinical implications of PD-L1 expression in the context of KRAS mutations.
Abstracts

Session SC28: Novel Clinical Trial Designs
Wednesday, December 7, 2016 - 11:00-12:30

SC28.04 Adaptive Clinical Trial Designs
Vassiliki Papadimitrakopoulou
Thoracic/Head & Neck Medical Oncology, MD Anderson Cancer Center, Houston/TX/United States of America

Interest in adaptive design study methods stems from the principle that these methods hold promise for improving drug development compared to conventional study design (i.e., non-adaptive) methods. The theoretical advantages of adaptive designs are that (1) they provide similar information more efficiently by reducing sample size and total cost, (2) increase the likelihood of success on the study objective, treating more patients with more effective treatments or (3) lead to better improved appreciation of the effects of therapy such as dose-response relationship or subgroup effects, for example identifying efficacious drugs for specific subgroups of patients based on their biomarker profiles, which may also lead to more impactful subgroups. Adaptive trial designs use accumulating data to modify the ongoing trial without undermining the integrity and validity of the trial. They also hold the potential for shortening the time for drug development. Several aspects of these trials including the dose-finding scheme, interim analysis, adaptive randomization, biomarker-guided randomization, and seamless designs will be discussed.

Many, but not all adaptive designs are devised under the Bayesian framework incorporating principles such as (I) obtaining the prior distribution; (II) collecting data to calculate the data likelihood; and then (III) computing the posterior distribution. The Bayesian framework provides an ideal statistical framework for adaptive trial designs (1, 2).

Examples of trials conducted with adaptive designs include the BATTLE and BATTLE-2 trials and ISPY-2. The basic principle is that patients enrolling earlier in a trial are used to inform how subsequent patients are treated, thus improving the efficiency of the study; this means that fewer patients are required to achieve the same answers regarding safe dosing and/or efficacy. The BATTLE and BATTLE-2 trials are prime examples of this approach. Both trials have implemented adaptive randomization schemes to assign patients to the more efficacious treatments based on their biomarker-guided profiles, and use interim analyses to monitor the efficacy outcomes during the trial.

The BATTLE trial (3, 4) enrolled patients with stage IV recurrent non-small cell lung cancer, employing a primary endpoint of eight-week disease control rate, as a binary outcome. Four targeted therapies, erlotinib, vandetanib, erlotinib plus bevacizumab, and sorafenib were evaluated, with one therapy targeting each of four biomarker profiles and it used an adaptive randomization scheme to allocate patients to the different treatments; hence, patients had higher probabilities of being assigned to better treatments based on their biomarker profiles. The trial showed that adaptive design could work in a complex trial that assessed multiple drugs and biomarkers and required tissue collection and biomarker analysis. Based on the findings of the BATTLE trial, a follow-up BATTLE-2 trial (5) was started, that evaluated four treatment regimens, erlotinib, sorafenib, erlotinib plus MK2206, and MK2206 + AZD5363 in a two-stage design with adaptive randomization. The first stage was completed with 200 patients. Biomarker selection was planned in 3 steps: training, testing and validation. In the training step, 10-15 potential prognostic and predictive markers were selected from the previous BATTLE experience, cell line data, and relevant literature information. In the testing step, the selected markers were tested using the data acquired from stage 1 of the BATTLE-2 trial. In the validation step, the markers selected in the first stage of the BATTLE-2 trial are used for adaptive randomization in the second stage of BATTLE-2. In BATTLE-2, we pre-specified an extremely limited set of markers and our intent was to use the first half of the study (200 patients) to conduct prospective testing of biomarkers/gene signatures. Predictive markers were to be used to guide patient assignments in the second half of the study. Although the design theoretically provided advantages, since clear predictive markers did not exist for any of the treatment Arms, activity was modest yielding no new predictive markers and not warranting further exploration. The ISPY-2 trial (6) is a multicenter phase II trial in the neoadjuvant setting for patients with breast cancer. The primary end point is pathologic complete response (PCR) at the time of surgery. The patient population is partitioned into ten subgroups depending on hormone-receptor (HR) status, HER2 status and Mamman Print signature. Experimental drugs are added to neoadjuvant therapy with the overall goal to prospectively learn as efficiently as possible which patients respond to each experimental treatment based on their biomarker profiles. Adaptive randomization with interim analysis is used within each biomarker subgroup, with the treatments that are performing better within a subgroup being assigned with greater probability to patients belonging to that subgroup. The phase II drug-screening stage is followed by a phase III confirmatory stage. The ISPY-2 trial has recently shown that two promising drugs improve response rates in specific biomarker subsets and has graduated these two drugs veliparib and neratinib for further development (7). The pharmaceutical industry and regulatory agencies are therefore very interested in adaptive designs because of their potential advantages and because they reflect medical practice in the real world.

To recapitulate, incorporation of adaptive designs in carefully designed and executed trials can enhance drug development, provide greater benefit to the enrolled patients, and effectively address many research questions of interest. These designs require deep understanding of theoretical statistical methodology, extensive modeling with simulations, specialized software and robust databases. Continued implementation in trials with guidance from regulatory agencies and innovative methods will contribute towards progress in therapeutics.


Keywords: adaptive designs, clinical trials
With limited resources for health, Low and Middle Income Countries (LMICs) struggle to guarantee all members of their society good cancer treatments, especially the innovative but expensive cancer medicines (2). Cancer is a leading cause of death in Thailand, which is an upper-middle income country in South-East Asia. From 2003 to 2011, the mortality rate from cancer rose from 78 to 95 per 100,000 populations. Since the Thai NLEM was first introduced in 1981, only cost, safety, and efficacy were considered as criteria for inclusion whereas effectiveness was added to the list of criteria in 2004. Since 2008, economic evidence has become important for the Sub-committee of the NLEM to justify the newly costly medicines such as type E2 to be included in the list of NLEM. As of 2009, the NLEM can be divided into six categories, which are A, B, C, D, E1, and E2. Type A: Basic medicines that every health facility must make available Type B: Alternative, second line medicines of those in category A Type C: Medicines prescribed only by specialists Type D: Medicines used only for particular indications and diseases Type E1: Medicines used only for special or vertical programs Type E2: Medicines that are high costs but are important for particular groups of patients. Health Care Coverage for Thai residences are divided into 3 categories: 1. Universal Coverage Scheme (UCS) Cover 75% of Thai population 2. Social Security Scheme (SSS) Cover 9% of the private sector employees, excluding dependents 3. Civil Servant Medical Benefit Scheme (CSMBS) Cover 9%. Government employees plus dependants (parents, spouse and up to two children age <20) The CSMBS has covered most of the cancer drugs including the expensive drugs, however UCS and SSS have covered only drugs listed in the NLEM; thus there are unmet needs for cancer patients with these two healthcare schemes. Thai government set up several policies to enable access to the cancer drugs such as Compulsory Licensing, Pooling purchasing (price negotiation), Social marketing arrangement (price negotiation), and E2 access program. Several pharmaceutical companies provide their own schemes for patients who are willing to pay for the drug by themselves (patient access program) even with all the programs available, the problem of accessibility of costly anticancer drugs still persists. There should be more input into this problem. References: 1. Kanavos P, Das P, Duraiyar V, Lagir, A, Abegunde DD (2010) Options for managing high cost medicines in the public and private sector, family and personal resources to deliver cost effective and affordable cancer care. The ESMO-MCBS is an important first step to the critical public policy issue of drug in cancer care, helping to frame the appropriate use of resources and personal resources to deliver cost effective and affordable cancer care. The ESMO-MCBS Scale (ESMO-MCBS) is a rational, structured and consistent approach to derive a relative ranking of the magnitude of clinically meaningful benefit that can be expected from a new anti-cancer treatment. The ESMO-MCBS is an important first step to the critical public policy issue of drug in cancer care, helping to frame the appropriate use of resources and personal resources to deliver cost effective and affordable cancer care. The ESMO-MCBS scale incorporates a dual rule method taking into account the variability of the estimated HR from a study, the lower limit of the 95% Confidence Interval (CI) for the HR is compared to specified threshold values; and second the observed absolute differences in treatment outcome compared to the minimum absolute gain considered as beneficial. Different candidate threshold values for HR and absolute gains for survival, DFS and DFS, adjusted to represent as accurately as possible the expert opinion of the oncology community, have been explored through extensive simulations. In all forms HR thresholds refer to the lower limit of the 95% CI, analogous to evaluating null effect by the upper limit of the 95% CI, and the performance of the evaluation rule based on the lower limit of the 95% CI of HR, was compared to the simpler rule of using a cut-off for the point estimate of HR, in conjunction with the additional rule on the minimum absolute gain in treatment outcome. The simulation resulted in different HR thresholds and corresponding power, and the proposed approach to use the lower limit of the 95% CI which takes into account the variability of the estimate. The concept that small studies generate wider confidence intervals is real and justified, however in the ESMO-MCBS v1.0 all high grading scores in a non-curative setting incorporate both HR and absolute gain to mitigate against overvaluing small studies with wide HR. This structured and disciplined approach to deriving estimates of clinically meaningful benefit from published data can be used in a range of settings: it can help public policy-makers advance “accountability for reasonsableness” in resource allocation deliberations, contribute to the formulation of clinical guidelines, in the education of help clinicians through the relative merits of competing relevant therapeutic options in situations in which there is no direct comparative data and grading may also be of benefit when explaining the relative merit of therapeutic options to patients and their families. Finally ESMO-MCBS may be of use to editors, peer reviewers and commentators in considering the clinical significance of research findings from randomised clinical studies, cohort studies and meta-analyses with statistically significant positive findings. Experience accrued in evaluating trials in the management of non small cell lung cancer have been critical in the development process of v1.0, with particular regard to the interpretation of PFS is studies with extensive crossover on progression that precludes meaningful OS survival results. In this cohort of studies, the inclusion of QoE evaluation was able to generate confirmatory secondary evidence to support the clinical significance of the PFS findings. The proliferation of new anti-angiogenic targeting NSCLC with specific mutations that have been approved on the basis of Phase I-II data have challenged the working group to expand the scope of the scale to include single arm studies. This new subscale will be among the amendments in the planned revision that is under development and scheduled for publication early next year. 1. Cherny NI, Sullivan R, Dafni U et al. A standard approach to generic, valid treatment to stratify the magnitude of clinical benefit that can be anticipated from anti-cancer therapies: the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS). Annals of oncology 2015, 26: 1547-1573.

Keywords: ESMO, Value, Clinical Benefit

SC29: ACCESS, VALUE ASSESSMENTS AND AFFORDABILITY OF NOVEL TREATMENTS WEDNESDAY, DECEMBER 7, 2016 - 11:00-12:30

SC29.05 THE THAI EXPERIENCE TO OVERCOME HIGH COST DRUG IN

CANCER
Sumitra Thongprasert
Oncology, Bangkok Chiangmai Hospital, Chiangmai/Thailand

Advances in modern technologies allow for an increasing opportunities in surgical and medical education. The main advantages for e-learning process are: accessibility and flexibility. A range of platforms offers educational and training programs accessible at work or home with total temporal and spatial freedom. Trainees are allowed to access their learning environment at a convenient time and pace. The learning can be repeated as desired. Through e-learning it is possible to introduce new topics or refresh the knowledge delivered during traditional training. The learning process is supported by a variety of media to suit different learning styles. This is a great advantage in surgical training where the trainee should be familiarized with a variety of surgical techniques and equipment. The main disadvantages of e-learning are that it is often time-consuming, it requires investment in computer equipment and software, and that it requires self-discipline and motivation. The main advantages of e-learning in thoracic oncology are: accessibility and flexibility. A range of platforms offers educational and training programs accessible at work or home with total temporal and spatial freedom. Trainees are allowed to access their learning environment at a convenient time and pace. The learning can be repeated as desired. Through e-learning it is possible to introduce new topics or refresh the knowledge delivered during traditional training. The learning process is supported by a variety of media to suit different learning styles. This is a great advantage in surgical training where the trainee should be familiarized with a variety of surgical techniques and equipment. The main disadvantages of e-learning are that it is often time-consuming, it requires investment in computer equipment and software, and that it requires self-discipline and motivation.
The goal of scientific organizations is to facilitate progress in specific areas through promotion of research, training, and education. In some instances, the scientific area may be a single discipline such as medical, surgical or radiation oncology, pathology, radiology and so on. In some instances, the scientific area may be a single geographic region such as Europe, North America or Asia. Examples of such organizations would be the European Respiratory Society (ERS), the American College of Radiology, the College of American Pathology (CAP) and many, many others. In some instances the organization might be working on a single project like research grants and in other instances the organization might focus on education of the public and in public programs such as prevention. In some instances the organization may conduct research or may solely sponsor research to be done by others. Some scientific organization chose to develop guidelines for clinical care. All of these efforts are important and different organizations focus on different aspects of a problem. In this presentation I will focus my attention on The International Association for the Study of Lung Cancer (IASLC) since it is the sponsor of the World Conferences on Lung Cancer and since is programs are dedicated to reducing the worldwide burden of lung cancer.

The IASLC was organized in 1974 it was recognized not only that lung cancer was the leading cause of cancer death worldwide and the most preventable. When the IASLC was organized in 1974 it was recognized not only that lung cancer was the leading cancer killer but also that it would take an international and multidisciplinary effort to make progress. The very international and multidisciplinary nature of the IASLC set it apart from other organizations. Many of the unique contributions of the IASLC rely on these differentiating aspects. For example, the IASLC has contributed all the cases and evaluation of the world wide lung cancer, mesothelioma and thymoma TNM staging classifications. The IASLC Pathology committee has formulated the changes to the pathological classification of all the lung cancers that have been designated the IASLC has worked with other organizations such as the College of American pathology and Association of Molecular Pathology to develop guidelines on molecular characterization of lung cancer. To enhance worldwide collaboration and education the IASLC began the World Conferences on Lung Cancer and rotated these conferences to different regions on the world. Originally, these conferences were held every 3 years as progress was slow but as research and research advances have quickened, the WCLCs are now held annually. In addition the IASLC sponsors regional meetings on a routine basis including the European Lung Cancer Conference (ELCC), the Latin America Lung Cancer Conference (LALCA), the Asia Pacific Lung Cancer conference and the Chicago Multidisciplinary Lung Cancer conference. The IASLC also sponsors workshops on various timely topics such as a conference on Small cell lung cancer held in 2015. To support its educational and research mission the IASLC publishes a scientific journal entitled Journal of Thoracic Oncology which has continually increased its circulation and impact factor. More recently, the IASLC has reinstituted a weekly newsletter and has published monographs on time issues such as ALK and PD-L1 testing. The IASLC has sponsored research grants especially for junior faculty and fellows to support and nurture the new research careers. The IASLC has also initiated travel fellowship awards for junior investigators and for young faculty from developing countries. The IASLC had worked with advocacy groups from around the world to provide information and support to these groups and to individuals and families affected by lung cancer. These efforts have led to a sharing of efforts and to publications directed to patients and their families. The IASLC’s tobacco committee has worked tirelessly to combat the worldwide tobacco epidemic. References: Tan DS, Yom SS, Tsaо MS, Pass HI, Kelly K, Peled N, Yung RC, Wistuba II, Yatabe Y, Unger M, Mack PC, Wynes MW, Mitsudomi T, Werner W, Yankelevitz D, Herbst RS, Gandara DR, Carbone DP, Bunn PA Jr, Mok TS, Hirsch FR. The International Association for the Study of Lung Cancer (IASLC) Consensus Statement on Optimizing Management of EGFR Mutation-Positive Non-Small Cell Lung Cancer: Status in 2016. J Thorac Oncol. 2016 Jul;11(7):946-63. doi: 10.1016/j.jtho.2016.05.008. Epub 2016 May 23. Review. Bunn PA Jr, Minna JD, Augustyn A, et al. Small Cell Lung Cancer: Current Recent Advances in Biology and Treatment. J Thorac Oncol. 2016 Apr;11(4):153-7. doi: 10.1016/j.jtho.2016.01.012. Epub 2016 Jan 30. Review. Goldstraw P, Chansky K, Crowley J, Rami-Porta R, Asamura H, Eberhardt WE, Nicholson AG, Groupe, Mitchell P. 

SESSION SC31: TOGETHER AGAINST LUNG CANCER – A STRATEGY FOR SUCCESS IN THE 21ST CENTURY

WEDNESDAY, DECEMBER 7, 2016 - 14:30-15:45

SC31.01 THE ROLE OF SCIENTIFIC ORGANIZATIONS

Paul Bunn, Jr.
Department of Medical Oncology, University of Colorado Denver, Aurora/CO/United States of America

The role of scientific organizations is to facilitate progress in a specific area through promotion of research, training and education. In some instances the scientific area may be a single discipline such as medical, surgical or radiation oncology, pathology, radiology and so on. In some instances the scientific area may be a single geographic region such as Europe, North America or Asia. Examples of such organizations would be the European Respiratory Society (ERS), the American College of Radiology, the College of American Pathology (CAP) and many, many others. In some instances the organization might be working on a single project like research grants and in other instances the organization might focus on education of the public and in public programs such as prevention. In some instances the organization may conduct research or may solely sponsor research to be done by others. Some scientific organization chose to develop guidelines for clinical care. All of these efforts are important and different organizations focus on different aspects of a problem. In this presentation I will focus my attention on The International Association for the Study of Lung Cancer (IASLC) since it is the sponsor of the World Conferences on Lung Cancer and since is programs are dedicated to reducing the worldwide burden of lung cancer. The IASLC was organized in 1974 it was recognized not only that lung cancer was the leading cancer killer but also that it would take an international and multidisciplinary effort to make progress. The very international and multidisciplinary nature of the IASLC set it apart from other organizations. Many of the unique contributions of the IASLC rely on these differentiating aspects. For example, the IASLC has contributed all the cases and evaluation of the world wide lung cancer, mesothelioma and thymoma TNM staging classifications. The IASLC Pathology committee has formulated the changes to the pathological classification of all the lung cancers that have been designated as a cancer killer. The IASLC has worked with other organizations such as the College of American pathology and Association of Molecular Pathology to develop guidelines on molecular characterization of lung cancer. To enhance worldwide collaboration and education the IASLC began the World Conferences on Lung Cancer and rotated these conferences to different regions on the world. Originally, these conferences were held every 3 years as progress was slow but as research and research advances have quickened, the WCLCs are now held annually. In addition the IASLC sponsors regional meetings on a routine basis including the European Lung Cancer Conference (ELCC), the Latin America Lung Cancer Conference (LALCA), the Asia Pacific Lung Cancer conference and the Chicago Multidisciplinary Lung Cancer conference. The IASLC also sponsors workshops on various timely topics such as a conference on Small cell lung cancer held in 2015. To support its educational and research mission the IASLC publishes a scientific journal entitled Journal of Thoracic Oncology which has continually increased its circulation and impact factor. More recently, the IASLC has reinstituted a weekly newsletter and has published monographs on time issues such as ALK and PD-L1 testing. The IASLC has sponsored research grants especially for junior faculty and fellows to support and nurture the new research careers. The IASLC has also initiated travel fellowship awards for junior investigators and for young faculty from developing countries. The IASLC has worked with advocacy groups from around the world to provide information and support to these groups and to individuals and families affected by lung cancer. These efforts have led to a sharing of efforts and to publications directed to patients and their families. The IASLC’s tobacco committee has worked tirelessly to combat the worldwide tobacco epidemic. References: Tan DS, Yom SS, Tsaо MS, Pass HI, Kelly K, Peled N, Yung RC, Wistuba II, Yatabe Y, Unger M, Mack PC, Wynes MW, Mitsudomi T, Werner W, Yankelevitz D, Herbst RS, Gandara DR, Carbone DP, Bunn PA Jr, Mok TS, Hirsch FR. The International Association for the Study of Lung Cancer (IASLC) Consensus Statement on Optimizing Management of EGFR Mutation-Positive Non-Small Cell Lung Cancer: Status in 2016. J Thorac Oncol. 2016 Jul;11(7):946-63. doi: 10.1016/j.jtho.2016.05.008. Epub 2016 May 23. Review. Bunn PA Jr, Minna JD, Augustyn A, et al. Small Cell Lung Cancer: Current Recent Advances in Biology and Treatment. J Thorac Oncol. 2016 Apr;11(4):153-7. doi: 10.1016/j.jtho.2016.01.012. Epub 2016 Jan 30. Review. Goldstraw P, Chansky K, Crowley J, Rami-Porta R, Asamura H, Eberhardt WE, Nicholson AG, Groupe, Mitchell P.
SC31: TOGETHER AGAINST LUNG CANCER – A STRATEGY FOR SUCCESS IN THE 21ST CENTURY

WEDNESDAY, DECEMBER 7, 2016 - 14:30-15:45

SC31.02 THE ROLE OF PATIENT ADVOCACY GROUPS

Bonnie Addario
Founder and Chair, Bonnie J. Addario Lung Cancer Foundation (ALCF)/cami, San Carlos/United States of America

The role of Patient Advocacy organizations in the oncology health care delivery ecosystem is ever evolving and has moved well beyond its original role of solely advocating for services, research, care and understanding. The current field of patient advocacy has its roots in the patient rights movement of the 1970s, being instrumental in getting a patient bill of rights accepted by the Joint Commission on Accreditation of Healthcare Organizations in 1972.

The transformation was further accelerated in 1991 with the formation of the FDA Patient Representative Program and has continued to expand over time with patient advocates now being involved in the entire care continuum. In this presentation I will focus my attention on examples of the ever evolving and transformation was further accelerated in 1991 with the formation of the FDA Patient Representative Program and has continued to expand over time with patient advocates now being involved in the entire care continuum. In this presentation I will focus my attention on examples of the ever evolving and expanding role of patient advocacy highlighted by projects developed and led by “partner” foundations the Bonnie J. Addario Lung Cancer Foundation (ALCF) and thelung-cancer-disparities-in-the-era-of-personalized-medicine 3. Leah Fine 1, Guneet Walia 2, Raymond U. Osarogiagbon 3; Addario Lung Cancer Foundation, San Carlos/United States of America, 1. Baptist Cancer Center, Memphis, TN/United States of America. The ALCF model represents a Standard of Care to the Community Similar to Academic and Research Centers. World Conference on Lung Cancer, Abstract 6334, December 2016 4. https://clinicaltrials.gov. 5. Barbara J. Gitlitz, Alicia Sable-Hunt, Steven W. Young, Andreas Kogelnik, Danielle Hicks, Deborah Morosini, Tiziana Vavala, Marco Bioni, 5. Lani Pai A, Silvia Novello, Geoffrey F. Duran 5. Bonnie Addario (in press). Employing Remote Web Consenting and Social Media to Facilitate Enrollment to an International Trial on Young Lung Cancer. World Conference on Lung Cancer, Abstract 4180, December 2016 6. https://www.openmednet.org/site/alcmi-goy.

Keywords: disparities, advocacy, accrual, Patients

TOGETHER AGAINST LUNG CANCER – A STRATEGY FOR SUCCESS IN THE 21ST CENTURY

WEDNESDAY, DECEMBER 7, 2016 - 14:30-15:45

SC31.03 THE ROLE OF MEDICAL JOURNALS

David Collingridge
The Lancet Oncology, The Lancet, London/United Kingdom

For many years the traditional peer reviewed medical journal was seen to be the only reliable place to obtain the latest advances in scientific medicine. But, with the advent of online repositories, information services and feeds, news services, preprint servers, data-sharing, and open access, to name just a few recent innovations, the role of the medical journal is changing. Whilst it is true to say that for many physicians, certain journals are still seen as an authoritative voice and a vital source of validated data to inform practice, this isn't the case for all—indeed, any reasonably reputable music industries, in which the online revolution has caused considerable upheaval—which many might argue has not resulted in a positive evolutionary change for the betterment of all stakeholders? The central tenet for any medical journal is publication of trustworthy data that have been thoroughly reviewed and challenged prior to publication to ensure the interpretation is accurate, honest, and will not cause harm if used in the real world. Moreover,
a good medical journal should be much more than this, and must show leadership; take risks; distill the most important information to a time-poor readership; provide innovative ways of linking disparate, but inter-related, strands of information to a readership that no longer reads cover-to-cover; and encourage scientific debate rather than simply reporting it. A good contemporary medical journal therefore needs to be more than just a mirror reflecting the latest research or thinking without contest: it must inform and drive research and clinical practice forwards. There are multiple ways in which this can be achieved. First, a journal must offer a impartial platform for presentation of data and discussion of ideas without prejudice, and ensure studies are reported rigourously, transparently, and honestly. The activities of an unconflicted editorial team and well-qualified peer reviewers are vital in this regard, as is the application of reporting standards to ensure all data and analyses are captured accurately. Second, journals have a responsibility to ensure the ethical integrity of everything they publish. Journals should be active members of independent ethics organisations and uphold the highest standards. If any suspicion of misconduct occurs surrounding a published article, reputable journals should always investigate such allegations, which often relate to issues such as: research conduct; reproducibility of data; unethical behaviour in the laboratory or institution; plagiarism; withholding of pertinent data and misreporting; conflicts of interests; authorship disputes; or compliance with prevailing governance structures. Academic institutions take these issues very seriously because of the ramifications for their own integrity, and thus journals and institutions must work together to root-out any misconduct and ensure the medical literature is trustworthy and organisations practice science and medicine of the highest standards. Third, journals can help further the practice of good science by taking a leadership role in forward-focused programmes. Recent examples include the team science programmes in the UK and USA, and the REWARD initiative. The UK Academy of Medical Sciences Team Science project has been focused on how biomedical researchers can be encouraged, supported, and rewarded for participating in team-based collaborations—editors and publishers are clear stakeholders in this debate, whilst the REWARD (Reduce research Waste And Reward Diligence) campaign encourages everyone involved in biomedical research to critically examine the way they work to reduce waste and maximise efficiency via five guiding principles: setting the right research priorities; using robust research design, conduct, and analysis; making sure regulation and management are proportionate to risks; ensuring all information on research methods and findings are accessible; and guaranteeing reports of research are complete and usable. Finally, a fifth role for medical journals is to take an dynamic part in advocating change, leading the direction of future research, and actively participating in health policy reform and in initiatives to promote universal access to medicine. The Lancet Oncology’s advocacy programme, for example, maps out the inequalities and inequities in health systems worldwide, and highlights deficiencies in all aspects of cancer care, health policy, structural organisation, and leadership. The programme offers an impartial platform that brings together thought-leaders from across different disciplines and organisations to offer solutions to those barriers that hinder provision of high-quality cancer control, irrespective of socioeconomic status or country of residence. The journal achieves this via specific, dedicated undertakings including Commissions, series of inter-related papers on specific themes, targeted articles, conferences, and events. The medical journal in the 21st century must evolve from being a simple record of research to an engaged stakeholder advocating and leading change in the practice of medicine. Journals should aim to be platforms that bring together communities and thought-leaders rather than disenfranchise groups in to silos. The world has never been as interconnected as it is today, and it is only by working together with a clear vision that journals, hand-in-hand with the communities they serve, will achieve the progress needed to promote the best research and health policies to improve healthcare for all.

Keywords: Medical publishing, Journals

SC31.04 THE POSSIBILITIES OF PRINT & SOCIAL MEDIA
Wolfgang Wagner
General News/science/medicine, Austria Press Agency Apa, Vienna/Austria

Lung Cancer – What media can/should do Oncology today is one of the main topics of health/medicine media coverage. With the advent of targeted and immunotherapies there’s been a shift towards presenting the rapid advances in this field. But contrary to topics like skin cancer, breast and colorectal cancer, lung cancer has stayed in the shadows of reporting until now. It has all been anti-tobacco campaigns often regarding smokers immoral, stigmatizing the patients. Late diagnosis and advanced disease plus bad prognosis have not made lung carcinoma a hot topic – and patient advocacy groups, often key players in getting topics into the broad public, are rare. What we have to do (besides non smoking campaigns): Produce valid information on the developing field of early diagnosis (in risk groups). Inform about advancing science and medical procedures to overcome this old nihilistic view of lung cancer as something too poor and bad to speak and write about.
SESSION MTE01: STRATEGIES TO IMPROVE TOBACCO CONTROL IN CENTRAL EUROPEAN COUNTRIES (TICKETED SESSION) 
MONDAY, DECEMBER 5, 2016 - 07:30-08:30

MTE01.01 STRATEGIES TO IMPROVE TOBACCO CONTROL IN CENTRAL EUROPEAN COUNTRIES
Martina Potschke-Langer1, Manfred Neuberger2
1German Cancer Research Center, Heidelberg/Germany, 2Preventive Medicine, Medical University of Vienna, Vienna/Austria

Tobacco use is the single most preventable cause of death and disease, especially of lung cancer. Approximately 1.6 million people in the WHO European Region die of tobacco-related diseases every year and the Region has the highest proportion of deaths (16%) attributable to tobacco use. Globally, Europe also has the highest prevalence of tobacco smoking among adults (28%), including one of the highest smoking prevalence rates among women (19%). In the meantime it is wellknown that a wide range of political decisions can stop the tobacco epidemic and reduce substantially smoking. According to the first health treaty in history, the WHO Framework Convention on Tobacco Control, following strategies are the most effective: raising cigarette prices through higher cigarette tax and combating illicit trade of cigarettes, protecting from secondhand smoke through comprehensive smoke-free laws, enforcing bans on advertising, promotion and sponsorship, utilizing public health warnings (pictures and text as big as possible) on tobacco packages and communicate the warnings through media/educational programmes and finally offering greater access to smoking cessation services. WHO Europe has established a database on countries of the WHO European Region showing the effects of the reduction in smoking prevalence as a result of implementing tobacco control policies. This presentation will analyse the current situation in this Region and showing the lessons learnt from past years with regards to future prevention of smoking.

Keywords: Strategies for effective tobacco control, WHO European region, especially Central Europe, Tobacco prevention

MTE01.02 STRATEGIES TO IMPROVE TOBACCO CONTROL IN CENTRAL EUROPEAN COUNTRIES
Manfred Neuberger
Preventive Medicine, Medical University of Vienna, Vienna/Austria

Up to now strategies of tobacco control, which were successful in Australia, North America and Western Europe, have been introduced only in few Central European countries. Implementing the EU Tobacco Product Directive Austria extended existing smoking bans, advertising bans and mailing bans for tobacco products to e-cigarettes. Still missing is an enforced smoking ban without exceptions in the hospitality industry, an advertising ban and display ban at point of sale, ban of vending machines, increase of age limit for buying any cigarettes and tobacco products to 18 years, enforcement of age control by regular test purchases, ban of free cigarettes (still allowed for introduction of new sorts), extension of warnings and ban of aromas to cigars and pipes, smoke-free hospitals and health care centers, smoke-free school premises without exceptions, smoke-free playgrounds and cars carrying children, smoke-free public transportation including stations, increase of tobacco tax earmarked for tobacco prevention (up to now only the quarantine has regular funding), stop of state funding for media violating article 13 FCTC, enforcement of article 5.3 FCTC (transparency law), obligatory TV air time (e.g. 90 min/month like in Turkey) for promotion of non-smoking, inclusion of smoking prevention and cessation in the curricula of health professionals, covering of counseling for smokers by health insurance, more frequent surveys on smoking prevalence, including cotinine tests for risk groups (pregnant women) and opinion leaders (journalists, health care workers), scientific evaluations of efficacy and effectiveness of smoking prevention and smoking cessation programs. Other Central European countries are facing similar problems. 13 of 16 federal states of Germany, the Czech Republic, Slovakia and most cantons of Switzerland did not succeed to pass and enforce smoking bans without exceptions in the hospitality industry. Germany is still violating the EU tobacco advertising ban and the Czech Republic recently failed to ban the use of water-pipes and e-cigarettes in enclosed spaces. Austria was the only Central European state, which ratified the FCTC smuggling protocol up to now. Switzerland did not even ratify FCTC and was abused by the tobacco industry as a base to sue and intimidate small countries like Uruguay for their progress in tobacco control. The Swiss government prepared amendments for the tobacco law without considering the EU tobacco directive. Tighter restrictions on tobacco advertising will probably be eliminated from the Swiss law. A ban of sponsoring by tobacco companies was not even considered within Switzerland. Lobbying in the Federal parliament and the government were able to block also comprehensive smoking bans. Fortunately, the country offers other political tools to progress, namely that counties can go for better policies, and Federal “initiatives” can be launched to bring issues to the ballots. In fact, 8 out of 26 Swiss Counties successfully adopted comprehensive smoking bans with no exemption. The Swiss parliament, however, was not even enabled to raise minimum prices of tobacco. If the Track-and-Tracing System of TPD-II is not joined, Switzerland might become a platform for international tobacco smuggling. In restaurants smaller than 80 square meters employers can still choose between smoking and non-smoking area. The largest progress of tobacco control in Switzerland was due to a tobacco prevention fund, financed from tobacco taxes (2.6 Rappen per pack of cigarette sold) since 2004. This fund finances also tobacco monitoring and smoking cessation (training of professionals). Swiss health insurance covers both counseling and pharmaceutical support of smoking cessation. The largest progress of tobacco control in Central Europe was seen in Hungary, which received the WNTD reward by WHO in 2013 and improved its ranking by the European Cancer Leagues from place 27 in 2010 to place 11 in 2013. Only in Hungary there is a total ban on smoking in all enclosed public places (except prisons and psychiatric wards) since 2012, and tobacco shops (reduced from 40 000 to 6 045) must not be entered below age 18. There is no tobacco advertising outside these shops, no vending machine for cigarettes and plain packaging was introduced in 2016. The main obstacle against improvement of tobacco control in the EU member states are the: tobacco industry and the subsidiarity principle in public health. The Green Paper of the EU “Towards a Europe free from tobacco smoke” showed policy options. 24 ministers of health voted on November 30, 2009 in favor of implementing the WHO-FCTC until 2012, but not the representatives of Austria, Czech Republic and the Republic of Ireland. Up to now the new Convention of FCTC and the EU Council Recommendation on Smoke-free Environments is voluntary. All countries of Central Europe except Switzerland ratified the FCTC treaty, but nonsmoker’s protection follows article 8 only in Hungary. In Central and Eastern Europe tobacco taxes and cigarette prices are much lower than in Northern and Western Europe. In a European ranking according to tobacco price increase by taxes, smoking restrictions at work and in public places, consumer information, tobacco advertising bans, health warnings and access to smoking cessation therapy, Austria, Germany, Cyprus, Czech Republic, Greece and Lithuania had the poorest score and would need help by more advanced EU members to reach Western standard. In summertime tobacco control in Central Europe needs enforcement of FCTC, in particular article 5.3, to stop interference of tobacco industry; application of strategies formulated by WHO (Monitor tobacco use & prevention, Protect from passive smoking, Offer help to quit, Warn about dangers, Enforce bans on ads & promotion, Raise tobacco tax and the World Bank (Curing the Epidemic: Governmental Reforms and the Economics of Tobacco Control); financing of tobacco prevention and cessation by tobacco taxes; comprehensive bans on advertising, promotion and sponsorship of tobacco products and e-cigarettes (including ban of vending machines, display ban at point of sale, plain packaging, stop of state funding for media violating article 13 FCTC); enforcement of smoke-free public places (without exceptions for hospitality industry), workplaces, schools, kindergartens, playgrounds, public transportation and private cars carrying minors and promotion of nonsmoking by schools and media campaigns.

Keywords: prevention, cessation, Central Europe, Tobacco Control

SESSION MTE03: BASICS OF MOLECULAR BIOLOGY FOR THE CLINICIAN (TICKETED SESSION) 
MONDAY, DECEMBER 5, 2016 - 07:30-08:30

MTE03.01 BASICS OF MOLECULAR BIOLOGY FOR THE CLINICIAN
Antonio Marchetti
Center of Predictive Molecular Medicine, University of Chieti, Chieti/Italy

The rapid development of molecular biology in recent years has allowed us to understand the main molecular alteration in the development and progression of lung cancer. The identification of molecular alterations in specific tumor genes that function as key drivers for neoplastic growth has laid the foundations for new therapeutic approaches with targeted agents. An accurate detection of target mutation is mandatory for an efficient treatment. The main steps involved in molecular diagnostics are: characterization of acquired resistance that makes cancer unresponsive to treatment. In many cases, through the acquisition of additional (secondary) mutations the tumor is able to acquire the heterogeneity which may enable it to adapt to various conditions of the microenvironment, including those determined by the effect of treatment with specific drugs. New generation drugs are constantly
under development to overcome tumor resistance and increase survival of lung cancer patients. In this process, a constant monitoring of the mutational status of the tumor is required. Different types of genetic alterations are involved in disease development, progression, and induction of resistance, including single nucleotide variants, indels, amplifications, fusions etc. Mutation detection before first line treatment is usually performed on tissue or cytological samples. Resected tumor samples, biopsies and cytological specimens are available in about 25%, 35% and 40% of NSCLC patients, respectively. At progression, a re-biopsy should be obtained to detect the emergence of resistance-inducing mutations. Transbronchial tissue biopsy is the most common sampling method used for re-biopsy. However, several factors limit the success rate of re-biopsy, such as the performance status of the patient, the difficulty of accessing some tumor sites, and the invasiveness of sampling methods and amount and quality of the biological material is insufficient for molecular analysis, circulating free DNA (cfDNA) can represent a valid alternative in selected patients. Liquid biopsies have several advantages over tissue or cells: they are less invasive, can be repeated over time, and have a more rapid turnaround time. However, there are some critical drawbacks that limit their potential. 1) cfDNA quantification in cfDNA is dependent on several clinicopathological parameters, including tumor type, tumor burden, and particularly tumor stage (a locally advanced tumor has a significantly lower probability to spread mutant DNA in the blood than a metastatic tumor); 2) a large amount of wild-type DNA circulates in the plasma with only trace amounts of the mutant allele; therefore, the analysis of genetic aberrations in cfDNA is challenging, requiring well standardized pre-analytical/analytical protocols and dedicated techniques with high sensitivity and specificity. Different technologies/protocols are required for the detection of the different genetic aberrations. Robust and sensitive chemomolecular biology techniques are nowadays available to detect mutations in driver genes before initiating a targeted treatment or to identify the emergence of secondary mutations at disease progression. The use of multimarker assays, and in particular next generation sequencing, is progressively becoming popular, allowing on one hand to reduce the working time, costs per single assay, and the amount of nucleic acids required for testing and increasing, in the other hand, throughput and overall quality. Recently, semi-quantitative or quantitative detection methods for the assessment of genetic aberrations in cfDNA have been developed with a number of potential clinical implications. An accurate quantification of mutated alleles in cfDNA during the first days of treatment could: a) complement or replace more expensive and invasive methods to assess response in treated patients; b) represent a new way to compare the effectiveness of different drug; c) be an additional tool to evaluate the best treatment regimen for patients. In addition, a periodic quantification of mutant burden during treatment could allow an early detection of resistance-inducing mutations for possible changes to therapy. 

Keywords: Targeted Therapies, Acquired resistance, Lung cancer molecular biology

SESSION MTE05: WHERE IS THE PLACE OF SURGERY FOR N2 DISEASE? (TICKETED SESSION)周一, December 5, 2016 - 07:30-08:30

MTE05.01 WHERE IS THE PLACE OF SURGERY FOR N2 DISEASE? Paul Van Schil 1, Corinne Fairen-Finot 2

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The diagnostic and management strategies for stage IIIA-N2 non-small cell lung cancer (NSCLC), which represents locally advanced disease with involvement of ipsilateral mediastinal lymph nodes, remain controversial despite results from several randomized controlled trials [1-2]. There are various reasons for this ongoing debate. First, stage IIIA-N2 represents a very heterogeneous patient population ranging from incidental discovery of positive N2 nodes during lung resection, to single mediastinal nodal involvement and bulky N2 disease where individual lymph nodes are hard to identify. In this setting, the precise diagnostic algorithm remains controversial. Currently, patients with proven or suspected lung cancer are mainly staged by integrated positron emission tomography – computed tomography (PET-CT). However pathological proof of nodal involvement should be obtained by a minimally invasive or invasive technique due to a relatively high rate of false positive nodes, owing cfDNA quantification (PET-CT). Secondly, the optimal restaging strategy after induction therapy is heavily debated. Thirdly, specific controversy relates to the role of surgery versus radiotherapy and the precise extent of resection after induction therapy. Randomized trials included different subsets of N2 disease making the interpretation of results difficult. As a result of the limitations of available data heated discussions have been taking place for several decades on the optimal treatment strategy for this subset of patients. When N2 disease is detected during thoracotomy, this is referred to as incidental, unsuspected, unforeseen or “surprise” N2 [4]. When found intraoperatively, a resection should be performed as long as it can be complete. Adjunctive chemotherapy prolongs survival and is currently recommended in this setting. However the role of radiotherapy remains controversial and is currently evaluated in the randomized LungART trial (NCT00410683) [5]. In quite a large subgroup of patients, N2 disease is suspected on PET-CT scanning and subsequently confirmed by mediastinoscopy or imaging techniques. Although the term “potentially resectable N2” is often utilized, no precise, internationally accepted definition is available. Most patients in this sub-group will be treated by concurrent chemo-radiotherapy alone or induction therapy followed by surgery or definitive radiotherapy. Whether induction chemotherapy yields better results and is a reasonable alternative when no N2 disease was studied in the recently published, randomised trial NCT00303771 of the Swiss Cancer League [6]. No significant differences were found. However, this study was not adequately powered to show non-inferiority between the two strategies. There are different restaging techniques to evaluate response after induction therapy. In contrast to imaging or functional studies, mediastinoscopy provides pathological evidence but is technically more difficult and less accurate than mediastinoscopy done prior to induction treatment [3]. An alternative approach consists of the use of minimally invasive staging procedures to obtain an initial proof of mediastinal nodal involvement. Currently, patients with confirmed or suspected stage IIIA-N2, and treatment strategies should be discussed with the patient. Salvage strategies for potentially resectable stage IIIA-N2 However bulky N2 disease is challenging, especially when bulky lymph nodes were initially present. At progression, a re-biopsy should be obtained to detect the emergence of resistance-inducing mutations for possible changes to therapy. Furthermore complete resection, which is a major prognostic factor, is mostly not achievable in this subset of N2 disease. The standard of care in patients with good performance status is concurrent chemoradiotherapy [1]. Of particular interest to thoracic surgeons is the relatively new concept of “salvage” surgery after full-dose chemo-radiotherapy in stage IIIA-N2 NSCLC [9, 10]. These patients present with recurrent or progressive locally advanced disease, in some cases complicated by an infected cavity, rendering surgical resection technically difficult. Furthermore, a systematic nodal dissection may be challenging, especially when bulky lymph nodes were initially present. In conclusion, although randomised controlled trials are available, no definitive answer can be provided regarding the optimal strategy for the diagnostic work up and treatment of the different subsets of stage IIIA-N2 disease. Every patient with locally advanced NSCLC should be discussed within a multidisciplinary tumour board including radiation oncologists and thoracic surgeons who have a large experience with major lung resections. The best available diagnostic and treatment strategies should be discussed with the patient and specific considerations should be used for the planning of treatment. The best available evidence suggests that surgery should be reserved for those centres having a large experience in thoracic surgery where a dedicated team is available as management of these patients requires multidisciplinary cooperation preoperatively, intraoperatively and postoperatively. References: 1. Eberhardt WE, De Ryuckersch D, Vander W, Le Péchoux C, De Leyn P, Hoffmann H.et al. 2nd ESMO Consensus Conference in Lung Cancer: locally advanced stage III non-small-cell lung cancer. Ann Oncol 2015; 26:1573-88. 2. Eberhardt WE, Pöttgen C, Gauler TC, Friedel G, Veit S, Heinrich V et al. Phase III study of surgery versus definitive concurrent chemoradiotherapy boost in patients with operable stage IIIA-N2 and selected IIIB non-small-cell lung cancer after induction chemotherapy and concurrent chemoradiotherapy (ESPAUFE). J Clin Oncol
SESSION MTE06: RADIOTHERAPY TECHNIQUES IN LUNG CANCER (TICKETED SESSION) MONDAY, DECEMBER 5, 2016 - 07:30-08:30

MTE06.01 RADIOTHERAPY TECHNIQUES IN LUNG CANCER
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Recent Advances in Radiation Treatment Technique for Lung Cancer Lung cancer is the leading cause of cancer-related death in the United States and throughout the world. Advancement of Radiation Treatment have been paralleled by the development of adjuvant chemotherapy and avoidance of normal tissue which associated with volume and dose. We can cure most of early lung cancer if it is well staged early cancer and targeted correctly by stereotactic body radiation therapy (SBRT). Because of high dose per fraction, technical aspects and quality assurance to deliver the radiation to the tumor precisely and avoid high dose of radiation to the critical surrounding normal tissue are critical issues organs in addition to controlling tumor motion. Technologic advancements of imaging and radiotherapy to conform the gross target volume (GTV) with margins but adequate critical targeted volume (CTV) and planning tumor volume (PTV) considering daily set-up variations which are supposed to minimize the dose to normal tissues. We have tried to answer higher radiation dose improve survival by the RT0G 0617 which compared overall survival after standard-dose versus high-dose intensity-modulated radiation therapy (IMRT) or three-dimensional conformal radiation therapy (3D-CRT) with concurrent chemotherapy +/- cetuximab for patients with inoperable stage III non-small-cell lung cancer.

Keywords: Advances, Technique, Lung Cancer

MTE06.02 RADIOTHERAPY TECHNIQUES IN LUNG CANCER
Martin Stuchke, Christoph Pöttgen
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Dose escalation with conventional fractionation and concurrent platin-based chemotherapy within the RT0G 0617 trial has failed to show a survival benefit. Proton therapy has failed to show a reduction in radiation pneumonitis in comparison to intensity modulated proton radiotherapy at the same total dose according to the NCT 00915005 trial. Randomized trials for comparison of IMRT and 3D conformal radiotherapy are lacking. While two-year OS, progression-free survival, local failure, and distance metastasis were not different between IMRT and 3D-CRT, IMRT was associated with fewer grade 3 or greater pneumonitis (79% vs 5%, P = 0.039) and a reduced risk in adjusted analyses (odds ratio, 0.41; 95% CI, 0.17 to 0.96; P = 0.046). IMRT also produced lower heart doses (P < 0.05), and volume of heart receiving 40 Gy (V40) was significantly associated with OS on adjusted analysis (P = 0.006). Lung V5 was not associated with any toxicity equal or greater than grade 3, whereas lung V20 was associated with increased grade 3 or greater pneumonitis risk on multivariable analysis (P = 0.026). IMRT was associated with lower rates of severe pneumonitis and cardiac doses in NRG Oncology clinical trial RT0G 0617, which supports routine use of IMRT for locally advanced NSCLC.

Keywords: Radiation, Future, IMRT, Proton Therapy, Advances, Lung Cancer

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and molecular targeted therapies are emerging as combination partners with radiotherapy in selected tumors. Proper patient selection criteria resulted long term survival as high as 30-45% in multivcenter prospective trials in locally advanced NSCLC. These advantages have to be bundled into new radiotherapeutic concepts and tested against the standard of conventional fractionated radiotherapy up to 60 Gy and simultaneous chemotherapy in future well designed randomized trials.

Keywords: dose painting, dose escalation, image guidance, IMRT

SESSION MTE08: IMMUNOTHERAPY IN EARLY AND LOCALLY ADVANCED NSCLC: CHALLENGES AND PERSPECTIVES (TICKETED SESSION)
MONDAY, DECEMBER 5, 2016 - 07:30:08:30

MTE08.01 IMMUNOTHERAPY IN EARLY AND LOCALLY ADVANCED NSCLC: CHALLENGES AND PERSPECTIVES
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The demonstration that therapies directed at the programmed death-1 (PD-1) receptor or its ligand (PD-L1) result in durable responses and improved survival in a number of solid tumours including non-small cell lung cancer has awakened interest in cancer immunotherapy. The activity of PD-1/PD-L1 therapy in NSCLC implies that endogenous T-cells can recognize antigens on tumour cells and eliminate those cancer cells. The success of checkpoint inhibitor therapy in the metastatic setting has led to a immunotherapy trials in early stage (adjuvant) and stage III NSCLC. This session will provide perspective on the current state and challenges facing immunotherapy in these settings. Current perspectives: The concept of using immunotherapy to prevent recurrence of NSCLC after resection of early stage NSCLC is not new. More recently, two randomized phase III trials of therapeutic cancer vaccine strategies have been completed in resected, early stage NSCLC (MAGRIT) or after chemoradiation in stage III disease (START). The MAGRIT trial (1) assessed the efficacy of an active, specific cancer immunotherapy (ASCI) against the MAGE A3 cancer testis antigen in completely resected stage IB-IIIA NSCLC. Tumors from more than 12,000 patients were screened for MAGE-A3 expression and 2312 patients whose tumours expressed MAGE A3 were randomized 2:1 to MAGE-A3 (ASCI) or placebo. The MAGRIT trial failed to meet its primary end-point of improvement in disease free survival with MAGE-A3 ASCI. The START trial(2) assessed a MUC1 vaccine in stage III NSCLC patients who had response or stable disease after standard chemoradiation. The chemoradiation had been delivered concurrently or sequentially. The modified intention to treat population included 1239 patients. The primary end-point was not met (adj. HR 0.88, 95% CI 0.75-103, p=0.123). Further development of this agent has been abandoned. The failure of these two large global phase III studies raises doubt about vaccine strategies used in isolation in early stage NSCLC. There are a number of possible explanations for these negative results (3). One of the primary reasons is that cancer vaccines, when used alone, fail to address the many immunosuppressive factors operating in the tumour microenvironment (TME). Clinical trials evaluating anti PD-1/PD-L1 therapy in early stage or locally advanced NSCLC have not yet reported results. The PACIFIC trial (NCT 20125461) is a randomized phase III trial of MEDA4736 versus placebo following concurrent chemoradiation in patients with stage III NSCLC. The primary outcome measures are OS and PFS. This trial completed accrual in April 2016 and has randomized more than 700 patients. In addition to the important efficacy outcomes, a number of exploratory objectives will assess tissue and blood for potential biomarkers. The Canadian Cancer Clinical Trials Group is assessing MEDI 4736 versus placebo in completely resected stage IB-IIIA NSCLC (NCT 22273379). This trial will randomize 1100 patients with the primary outcome measure being DFS in PD-L1 positive patients. PD-L1 positive is defined as >5% positive tumour cells. Immune Based Prognostic Markers: The TME consists of stromal cells including endothelial cells and fibroblasts and a number of immune cell types. Tumour escape immune recognition in large part by modulating the recruitment and function of various immune cells into the TME (4). A comprehensive review of the prognostic value of different immune cells in NSCLC has been reported (5). Two recent studies have separately assessed tumour lymphatic infiltrating (TLI) (6) or stromal CD8+ T-cell density (7) as potential prognostic markers in early stage NSCLC. Using the large, relatively homogenous population of curative resected NSCLC patients from the LACE-Bio collaboration, Brambilla et al examine the prognostic and predictive value of TLI. Patients were separated into discovery and validation sets. An independent LLI (50% stromal lymphocytes in tumour bulk) was strongly prognostic of favourable overall survival and disease free survival. Based on previous work, Donner et al selected stromal CD8+ Tumor infiltrating lymphocyte as the most promising immuno-based prognostic marker. Using four separate cohorts of curatively resected stage I-III patients, they established training and validation sets. Tissue microarrays were scored for stromal CD8 TLI’s; stromal CD8 TIL density was found to be an independent prognostic factor and retained significant prognostic impact within each stage. The value of PD-L1 as a prognostic marker in early stage NSCLC has many limitations. These studies are small, include heterogeneous populations, assess PD-L1 using different antibodies and scoring systems and included PD-L1 on tumour cells only or tumour cells and TIL’s. It is not surprising that these studies show conflicting results. Based on the available evidence, the prognostic value of PD-L1 expression in early stage NSCLC remains uncertain. The adjuvant trials of anti-PD/PD-L1 therapy currently being conducted may clarify the value of PD-L1 as both prognostic and predictive biomarkers in this setting. Challenges One of the fundamental challenges to developing effective cancer immunotherapies is our limited understanding of the human immune system in steady state and its response to stress. Animal models do not necessarily translate to humans. The Human Vaccines Project (8) is a global initiative that has as one of its primary objectives the decoding of the human immune system and providing a map of the human “immunome”. This private-public partnership uses state-of-the-art machine learning and technologies to elucidate the principles of immunogenicity to accelerate the development of new immunotherapies against infectious diseases and cancer. A second challenge is how best to target micrometastases in the adjuvant and locally advanced setting. While the primary tumor and metastatic lesions have many mutations in common, metastatic tumors possess mutations that are distinct from the primary. Do adjuvant therapies need to target the metastatic cascade and if so, which steps are the most susceptible to intervention? (9) The complex of the TME would predict that focusing on TIL’s or PD-L1 is likely to result in only modest improvements in outcome. Blank et al (10) argue that it will take a combination of biomarkers, the “cancer immunogram”, to determine the best approach in individual patients.References:
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Nature Reviews Cancer 2015; 16: 201-218
Science 2016; 352(6268): 658-660
Keywords: non-small cell lung, early stage, adjuvant, immunotherapy

SESSION MTE09: BIOMARKERS FOR TARGETED THERAPIES AND IMMUNE CHECKPOINT INHIBITORS IN ADVANCED NSCLC (TICKETED SESSION)
MONDAY, DECEMBER 5, 2016 - 07:30:08:30

MTE09.01 BIOMARKERS FOR TARGETED THERAPIES AND IMMUNE CHECKPOINT INHIBITORS IN ADVANCED NSCLC
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The targeted therapy based on genotyping has become an important treatment approach for advanced non-small cell lung cancer (NSCLC), especially adenocarcinoma. It is reported that nearly fifty to sixty percent of Asian patients with lung adenocarcinoma could have survival benefit from the first generation epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKI) and Anaplastic Lymphoma kinase (ALK)-TKI. However, the targeted therapy has apparently reached a plateau due to the drug resistance. The spatial and temporal heterogeneity of tumors are regarded as the foundation of both primary and acquired resistance. The studies show that the mechanism of acquired resistance to first generation EGFR-TKI is complicated, including T790M mutation, PI3KCA mutation, c-MET amplification, and histologic transformation from NSCLC to SCLC et al, some of which could co-exist in the same patient. Although the third generation EGFR-TKI targeted at T790M mutation has been proved with dramatic efficacy, most patients become resistant after 10 months of therapy, the
Targeted Therapies in Lung Cancer

SESSION MTE10: UNIQUE BIOLOGIC ASPECTS OF TOBACCO-CO-INDUCED LUNG CANCER (TICKETED SESSION)
TUESDAY, DECEMBER 6, 2016 - 07:30-08:30

MTE10.01 UNIQUE BIOLOGIC ASPECTS OF TOBACCO-CO-INDUCED LUNG CANCER
Mauro Papotti, Giorgio Scagliotti
OncoLgy, University of Turin, Orbassano Turin, Italy

Lung cancer is the leading cause of cancer death worldwide and cigarette smoking is a major causative environmental factor. Some unique biological profiles of tumors are associated to tobacco induced lung cancer, due to the unique smoking history, pathological and genetic features. Lung cancer in never smokers (up to 20% of cases worldwide) has been suggested to represent a distinct disease, compared to tobacco-induced lung cancer. Cigarette smoke is a mixture of more than 5000 chemical compounds, among which more than 60 are responsible for tobacco addiction, only, is also involved in tumor promotion among others) can activate multiple pathways, contributing to pulmonary carcinogenesis. While the biggest challenge of immunotherapy currently is to explore novel drug-resistant mutations through NGS of peripheral blood samples in future. Checkpoint inhibitors have been studied and utilized in various cancers, which has changed the perennially stagnant situation of immunotherapy and opened a new chapter in the treatment of cancers. The results varied from different agents of PD1/PD-L1 inhibitors and results of different trials. For instance, PD-L1 expression was associated with response to Nivolumab in patients with lung adenocarcinoma, while this kind of relationship was not observed in squamous cell NSCLC. The inconsistency between different drugs may be attributed to the heterogeneity of PD-L1 expression, the unstandardized sample collecting and storing, and issue in IHC evaluation system. So the future investigation should lay more emphasis on overcoming tumor heterogeneity, standardization and optimization of detection techniques and sample collections, based on which we are looking forward to more accurate predictive biomarkers. The microenvironment should be equally important as the foundation of precision medicine for cancer. More and more studies show that mutation loads of somatic cells contribute to immunogenicity of tumors, so as to be associated with the efficacy of checkpoint inhibitors. One research showed that different types of mutations, such as EGFR mutation, ALK fusion gene and PI3KCA mutation, possess different levels of mutation loads. And another research indicated that lung adenocarcinoma with higher neoantigen-load responded better to checkpoint inhibitors than the lower ones. There has been a study to calculate mutation loads and neoantigens in adenocarcinoma or squamous carcinoma through whole Exome sequencing based on the Cancer Genome Atlas (TCGA). The future studies should pay close attention to exploring the dynamic change patterns of mutation loads and neoantigens prior and during the treatment strategies, including PD-1/PD-L1 inhibitors immunotherapy, targeted therapy and traditional chemotherapy, and also to investigate the role of other regulatory immune factors in tumor microenvironment, to further establish the predictive system for immunotherapy integrating PD-L1, PD-L2, TIL mutation loads of somatic cells, and neoantigens which are in great expectations.

Keywords: Immune checkpoint inhibitors, biomarker, dynamic change, Targeted Therapies
and progression with anti-apoptotic and indirect mitogenic properties (Toniini et al. Future Oncol 2013;9:649-55). Preclinical models were employed to define epigenetic alterations and gene expression profiles in respiratory epithelia exposed to cigarette smoke condensate. In a study, smoke condensate significantly repressed miR-487b, that directly targets several genes, including SUZ12, BMI1, WNT5A, MYC, and KRA. Such repression correlated with overexpression of the above targets in lung cancer and coincided with DNA methylation within the miR-487b genomic locus, indicating this molecule as a tumor suppressor microRNA silenced by epigenetic mechanisms during tobacco-induced pulmonary carcinogenesis. These findings may potentially pave the way for DNA demethylating agent treatment, in order to re-activate miR-487b in lung cancer therapy (Xie et al. JCI 2013; 123:1241-61).

Among other effects of cigarette smoking, a syngery was described with the aryline receptor (AHR), which is specifically responsible for genome-induced carcinogenesis through incompletely understood mechanisms. It was reported that smoking induces AHR activating ligands, which in turn induced adrenomedulin both in vitro and in vivo, thus significantly contributing to the carcinogenicity of tobacco-activated AHR. These effects were not reproduced in fibroblasts and mimicking the aryline receptor receptor (Portal-Nuñez et al. Cancer Res 2012, 72:S790-800). Genetic factors involved in tobacco-induced lung cancers have been widely investigated to determine the genetic susceptibility to lung cancer, including epigenetic alterations (Fujimoto et al. PlosOne 2010;5:e18847. Liu et al. Oncogene 2010;29:6530-65). In addition, tobacco-related histotypes has provided a relatively complete map of most common alterations in each tumor. The above genetic alterations are observed in all histological subtypes of lung cancer (Spitz et al. Cancer Epidemiol Biomark Prev 2012; 21:1213-21).

Therefore, in inflammation pathway associated genes, as well as a number of genetic polymorphisms have been identified as putative candidates to facilitate early lung cancer development. The effects of these polymorphisms on lung cancer development risk have been investigated, with inconsistent results. Most currently identified polymorphisms involve genes encoding proteins associated with the metabolic processing of tobacco smoke carcinogens and the repair of mutations induced by those carcinogens. Mutations in chromosomal Sp5.33, Sp21, and Sp25 were identified, being the former specifically associated to a higher risk for adenocarcinoma (Yokota et al. Adv Cancer Res 2010;109:51-72).

Regarding inflammation pathway genes, analyzing a comprehensive panel of over 11,000 inflammation pathway single-nucleotide polymorphisms (SNP), six SNPs were significantly associated to a higher risk of lung cancer development, including two SNP variants in former smokers (BCL2L1A) and in current smokers (IL2RB) (Spitz et al. Cancer Epidemiol Biomark Prev 2012; 21:1213-21).

The above genetic alterations are observed in all histological subtypes of lung cancer with several differences, especially between small cell lung cancer (SCC) and non-keratinising SQCC (P40 and/or CK5/6 positive). This has already allowed more appropriate decisions in relation to adjuvant therapy and better classification of those that do to solid adenocarcinoma (TTF-1 positive).

Abnormalities in the 2015 WHO classification of lung tumors (TICKETED SESSION)

SESSION MTE11: THE CLINICAL IMPACT OF THE 2015 WHO CLASSIFICATION OF LUNG TUMORS (TICKETED SESSION)

TUESDAY, DECEMBER 6, 2016 - 07:30-08:30

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There are many important changes in the 2015 WHO classification of lung tumors, reflecting the numerous advances in tumor genetics and therapy over the past decade. Many have been in the field of adenocarcinoma, with discontinuation of the term bronchioloalveolar carcinoma and the concept of stepwise progression accepted for adenocarcinoma. Adenocarcinoma in situ (AIS) is a small (less than 3 cm in diameter), pure endobronchial adenocarcinoma, minimally invasive adenocarcinoma (MIA) is also a small adenocarcinoma but has small invasive areas less than 5 mm across. As both entities have a very favorable outcome, with an expected 5-year survival rate of 100%, AIS and MIA are targeted for resection and likely detected by low-dose CT screening. High-resolution (HR) CT demonstrates these tumours as a pure ground glass nodule (GGN) or a part-solid nodule (PSN), being closely related with their pathological features. Therefore, AIS and MIA can be assessed by HR-CT. However, the size of the solid component in HR-CT images does not necessarily correlate with extent of histological invasion, since features such as alveolar collapse and fibrosis are also included in the solid part demonstrated by HR-CT. Although the new WHO classification defines the histological criteria for MIA invasion, the degree of inter-observer agreement regarding the histological definition of invasion in MIA has still not been fully studied, and a consensus trial will be needed in the near future. More advanced adenocarcinoma is subdivided into five categories: lepidic, papillary, acinar, solid and micropapillary. Therefore, the presence of solid and/or micropapillary adenocarcinoma should be reported, even if the predominant component is lepidic, papillary or acinar adenocarcinoma. These patterns also predict response to adjuvant chemotherapy, and the above changes overall have also led new proposals for both clinical and pathological classification.

The 2015 WHO classification of lung tumors has been shown to correlate with molecular data. Therefore, the molecular data allow more appropriate decisions in relation to adjuvant therapy and better defined subgroups for studies into molecular characterisation and the search for potentially treatable targets. This classification is now restricted to resected tumours that lack clear morphological and immunohistochemical differentiation, with reclassification of those that are not solid adenocarcinomas (pure ground glass and non-keratinising SCC (P40 and/or CK5/6 positive) and non-keratinising SCC (P40 and/or CK5/6 positive). This has already been correlated with molecular data.

For solid SCC, classification is simplified to keratinizing, non-keratinizing and basaloid subtypes, with the non-keratinizing tumours ideally requiring immunohistochemical confirmation. Criteria for diagnosing NE tumours remain essentially unchanged but these tumours are now grouped in one category, with further subdivision into carcinoids, and large cell neuroendocrine carcinoma and small cell carcinoma. Molecular studies based on these definitions are already identifying interesting subgroups. In relation to rarer entities, the definition of carcinoid tumours is also provided to have clinical relevance in terms of correlating with potential therapies, both in relation to specific molecular abnormalities (exon 14 skipping mutations) and immunomodulatory therapy with high levels of PD-L1 expression. Molecular characterisation is also increasingly important in the accurate diagnosis and potential treatment of other rare tumours such as NUT carcinoma, a tumour characterized by immunohistochemical reactivity of myofibroblastic tumours (ALK and ROSI/RET gene rearrangements).

A classification system for small biopsies and cytology is provided for the first time, with emphasis on integration of molecular testing and usage of a limited number of. For mucosal chemotherapy is also often needed (Table 1). The presence of such a system for the first time provides a system for consistent classification of the majority (unresectable) of lung cancer cases, both in terms of clinical management, assignment to pathways for molecular and immunomodulatory tests and for pathological classifications, and for assessment of the results of clinical trials that may sometimes be confounded by inappropriate subgrouping. The book also emphasizes how to obtain the greatest value from small sample via efficient usage and avoidance of inappropriate testing.

Table 1: Classification of non-small cell lung carcinoma in small biopsies and cytology specimens when there is no morphological evidence of differentiation.
Abstracts

SESSION MTE12: CLINICALLY RELEVANT SIGNAL TRANSDUCTION PATHWAYS (TICKETED SESSION)

TUESDAY, DECEMBER 6, 2016 - 07:30-08:30

MTE12.01 CLINICALLY RELEVANT SIGNAL TRANSDUCTION PATHWAYS

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Up to a decade ago, the main non-surgical treatment modalities in oncology have been cytotoxic chemotherapy and/or radiation therapy. These therapies are aimed at inducing DNA damage, thus selectively killing the highly proliferative cancer cells. More recently, new therapies are targeting signaling pathways that are critical to support cancer cell proliferation and/or survival, including micro-environmental factors that sustain tumor. The first part of our presentation will review pathways operating mainly in the tumor cells, and how they constitute targets for lung cancer therapies. The second part will focus on the vasculature mechanisms in primary and metastatic lung tumors, anti-vascular drugs, potential biomarkers and on mechanisms through which tumors can become resistant to anti-vascular drugs. DNA Repair Pathway: Genomic DNA encodes all biochemical processes that drive cellular function and biology. Extensive damage to DNA encoding proteins/enzymes involved in cell proliferation will result in cell cycle arrest and cell death. DNA damage may also induce replicative stress and mutations, which leads to constitutive activation of oncogenes, or inactivation of tumor suppressor genes. DNA repair mechanisms are crucial for mitigating catastrophic chromosomal damage during DNA synthesis and replication, thus allowing tumor cells to survive chemotherapy or radiotherapy. New targeted anti-cancer agents being developed are those that inhibit the activity of critical molecules involved in DNA repair, or inhibit cell cycle checkpoint proteins that allow DNA repair mechanisms to occur. EGFR and downstream pathways: The proliferation of epithelial cells depends on growth stimuli arising from either factors produced by the tumor cells themselves (autocrine stimulation) or from antigen presented by the innate immune system. Epidermal growth factor receptor (EGFR) family members, EGFR (HER1) is highly expressed in ~90% of squamous cell carcinoma and in 60-80% of adenocarcinomas. EGFR has many ligands, including EGF, TGF-a, amphiregulin, HB-EGF, etc. Binding of the ligands to the EGFR induces homotrimerization and dimerization of EGFR and its family members, activates the cytoplasmic tyrosine kinase of the receptor, and promotes auto-phosphorylation. This sequentially leads to binding of SOS1, activation of downstream oncogenes. Inhibition of EGFR by monoclonal antibodies and small molecule kinase inhibitors have demonstrated clinical efficacy in subpopulation of NSCLC patients. Targeted agents against KRAS, BRAF and MEK are in clinical trials. MET, ALK, and ROS1 inhibitors: Other (RTKs) kinase receptors that may play an important role in lung cancers include hepatocyte growth factor (HGF) receptor MET and fibroblast growth factor receptor (FGFR) family members. In contrast to EGFR, the ligands for MET and FGFRs appear to be produced by the tumor stromal fibroblasts. While attempts to inhibit MET signaling pathway by neutralizing antibody have not been successful, recent data suggest that MET kinase inhibitors may be highly effective in patients with MET exon 14 splice mutations. Such mutations cause the loss of exon 16, which encode the Cbl binding site of the receptor, a crucial domain required for the degradation of MET receptor. The RTKs with close homology to MET are ALK and ROS1. Constitutive activation of ALK and ROS1 occurs by formation of new chimeric protein through translocation involving these genes. Inhibitors to ALK and ROS1 are now clinically approved for treatment of lung cancers that express fusion proteins resulting from the rearrangement of the ALK and ROS1 genes. PI3K/Akt/mTOR pathway: Aside from activating the MAPK pathway, tyrosine kinases can also activate the PI3K/Akt/mTOR pathway, which plays a crucial role in the survival of lung cancer cells. This pathway is commonly activated in NSCLC through amplification or activating mutation of the PIK3CA gene, or inactivation of PTEN by gene deletion, mutation or methylation. While there is intense research to develop targeted therapies that RAS, RAF, MEK and PI3K pathway. While the efforts have so far met little success, revealing the complexity of this pathway. There is also evidence that alternative RTK and PI3K signaling play an important role as bypass mechanisms for the development of resistance to EGFR inhibitors. Anti-angiogenic pathways: Angiogenesis is a key mechanism of new blood supply is required for tumor development. There was an overwhelming optimism initially that blocking angiogenic pathways would represent an effective treatment strategy in solid malignancies, including primary and metastatic lung tumors. However, clinical trials investigating anti-vascular drugs have been discouraging and disappointing. Survival benefit with anti-vascular strategies therefore requires a deeper knowledge of the clinical significance of the different angiogenic machineries that control lung tumors. VEGF (vascular endothelial growth factor) is the key molecular regulator of new tumor blood capillary formation (i.e. angiogenesis) and its high expression is associated with poorer survival in NSCLC. Bevacizumab, a humanized monoclonal anti-VEGF antibody, is currently approved for the first-line treatment of advanced stage non-squamous NSCLC in combination with chemotherapy. Ramucirumab (a full human monoclonal antibody against VEGFR2) has been approved for use in combination with docetaxel for the treatment of metastatic NSCLC patients who progressed at least once after platinum-based chemotherapy. Nintedanib (an oral RTK inhibitor against VEGFRs, platelet-derived growth factor receptors (PDGFR) and FGFRs in combination with chemotherapy has been approved by the EMEA in NSCLC patients with locally advanced, metastatic or locally recurrent lung adenocarcinoma after first-line chemotherapy. Additional anti-angiogenic strategies including vascular disrupting agents (VADs) to destroy the established tumor vasculature and other investigational antiangiogenic antibodies and small molecule RTK inhibitors are also under clinical testing for NSCLC therapy, though enthusiasm is tempered by concerns on drug resistance and modest overall survival benefit. Angiogenesis Resistance Mechanisms and Biomarkers: Unfortunately, resistance to anti-angiogenic therapies is poorly understood. The possible resistance mechanisms include increased intratumoral hypoxia, the activation of compensatory angiogenic machineries, the release of VEGF by endothelial progenitor cells and endothelial micromasses, the downregulation of target receptors in endothelial and/or tumor cells, limited tumor tissue drug penetration, and also a switch to an alternative...
vascularization mechanism such as intussusceptive angiogenesis or vessel-cooption. Reliable biomarkers for the prediction of response to antivascular drugs are also yet to be identified and clinically validated.

SESSION MTE13: BASIC IMMUNOLOGY FOR THE CLINICIAN (TICKETED SESSION)
TUESDAY, DECEMBER 6, 2016 - 07:30:00:30

MT1E3.02 BASIC IMMUNOLOGY FOR THE CLINICIAN
Edgardo Santos
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Lung cancer remains the number one cause of cancer-related death worldwide. Cancer immunotherapy nowadays has become not only a growing field but also a fascinating area as recent clinical trials have improved both PFS and OS in first line and second line treatment for patients with advanced NSCLC. The idea of immunotherapy in cancer is to modify the host immune system, so cytotoxic T-cells (CTCs) can recognize tumor-associated antigens (TAAs) as abnormal and be destroyed by an immune response. For many decades, we have tried unsuccessfully many vaccines against different lung cancer antigens. It was thought at one point that lung cancer was a non immunogenic tumor very different from melanoma and kidney cancers. Whole-cell vaccines (e.g. belagenpumatucel-L) and antigen-specific vaccines (e.g., CIMAvax, MAGE-A3, L-BPL25) showed just promising results in clinical trials, but failed to significantly improve clinical outcomes [1-4]. The main reason why vaccines failed is due to tumor escape mechanisms from host immune surveillance [5, 6]. One of these mechanisms was recently elucidated, checkpoint pathway. Lung cancer has been found to have high levels of CTLA-4 expression, programmed death-1 (PD-1), PD ligand 1 (PD-L1), B7-H3 and B7-H4 expression on tumor-infiltrating lymphocytes (TILs), and regulatory CD4+ T-cells (Tregs) [7, 8]. For many years, cancer immunology was centered on the adaptive immune system and T-cell activation. Stimulation of the T-cell response involves antigen presenting cells (APCs), or dendritic cells (DCs), expressing tumor antigens from the tumor microenvironment and presenting them to the T-cell receptor (TCR) on CD28 or CD4+CD8+ T-cells. Meanwhile, B7/CD80, or B7/CD86 on the APC, bind to CD28 on the T-cell in a costimulatory fashion to stimulate tumor-antigen specific T-cells to proliferate. However, cross talk between APCs and T-cells at the immunological synapse is regulated very closely and can be attenuated. One of the mechanisms involved in this attenuation signal is mediated by CTLA-4, which is also stimulated by the CheckMate 057 showed OS and RR in favor of pembrolizumab at a dose of 10 mg/kg and 2 mg/kg shown as an OS of 12.7 months (HR 0.51, p<0.001) and 10.4 months (HR 0.71, p<0.001); OS for docetaxel was 8.5 months. Noteworthy, OS was better in second line therapy. Herein, pembrolizumab at a dose of 10 mg/kg and 2 mg/kg shown as an OS of 12.7 months (HR 0.51, p<0.001) and 10.4 months (HR 0.71, p<0.001); OS for docetaxel was 8.5 months. Noteworthy, OS was better in patients whose tumors expressed PD-L1≥50%; these patients had an OS of 17.3 and 14.9 months when received pembrolizumab at 10 mg/kg and 2 mg/kg, respectively. Again, grade 3-5 treatment-related AEs were less common for both pembrolizumab doses than for docetaxel. Recently, press release on KEYNOTE-024 phase III study, reported OS in favor of pembrolizumab over platinum-based doublet in first-line therapy for advanced NSCLC patients with PD-L1 expression. The clinical results from KEYNOTE-024 may change the landscape of lung cancer treatment at first-line for advanced NSCLC. Also in development are the PD-L1 inhibitors which affect the interaction between PD-L1 and B7 and PD-L1 receptor and PD-L2, the later interactions are not affected by PD-L1 inhibitors. Atezolizumab and durvalumab have several phase III trials ongoing in first line for advanced NSCLC. Phase II trials for both compounds have shown promising results. The role of PD-L1 as predictive biomarker is still not well defined. PD-L1 expression is a dynamic process and it also varies as part of an adaptive immune resistance exerted by the tumor. There are other possible predictive biomarkers such as higher nonsynonymous mutation burden, molecular smoking signature, higher neo-antigenic burden, DNA repair pathway mutations, high levels of PD-L1 expression, T-helper type 1 gene expression, and others. There is no question that we must continue looking for a better predictive marker which can help us to determine the therapeutic benefit of PD-L1/PD-L1 inhibitors. References. 1. Nemunaitis J, Dillman RO, Schwarzenberger PD, et al. Phase II study of belagenpumatucel-L, a transforming growth factor beta-2 antisense gene-modified allogeneic tumor cell vaccine in non-small-cell lung cancer. J Clin Oncol. 24, 4721–30 (2006). 2. Gonzalez G, Combet T, Neninger E, Viada C, Luo A. Therapeutic vaccination with epidermal growth factor (EGF) in advanced lung cancer: analysis of pooled data from three clinical trials. Hum Vaccin. 3(1), 8-13 (2007). 3. Vansteenkiste J, Zielinski H, Linder, A, et al. 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Keywords: lung cancer, checkpoint pathway, Immunotherapy, PD-L1

SESSION MTE15: LYMPH NODE MAPPING IN LUNG CANCER (TICKETED SESSION)
TUESDAY, DECEMBER 6, 2016 - 07:30:08:30

MT1E5.02 LYMPH NODE MAPPING IN LUNG CANCER
David Waller
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The How and Why? The Aim will be to outline the various methods to map the extent of lymph node metastasis from a primary NSCLC and to assess the clinical application and implications of each intervention. The Aim will also be to highlight the following areas of clinical debate and controversial infection: Preoperative Non-invasive – Lymph node mapping which starts with simple Ultrasound guided cervical node aspiration cytology [1]. Can this be all that is needed in some advanced cases? Can computed tomography/ positron emission tomography (CTPET) be relied upon to obviate the need for invasive nodal mapping? Can newer techniques including CT lymphography [2] improve the accuracy of mapping? Does magnetic resonance imaging (MRI) have a role in preoperative lymph node mapping. Invasive – We will consider in detail the debate between endobronchial and endoluminal ultrasound (EBUS/EUS) and surgical lymph node mapping. What role, if any, does cervical mediastinoscopy have in addition to EBUS/EUS [3]? Does the sensitivity and specificity of more invasive surgical procedures like VAMLA [4] and TELMA contribute significantly to preoperative mapping? We will discuss why these investigations should influence primary therapy and which patients should undergo induction therapy and which should have primary resection. Evidence from the latest TMN revision suggests that mediastinal nodal disease needs more accurate mapping than previously appreciated. We will consider how many of these stages of mapping are required before making
a decision to operate and will propose a controversial algorithm for surgical treatment of N2 disease [5]. 2. Intraoperative We will discuss the arguments surrounding the necessary extent of intraoperative lymph node dissection. We will consider the relative merits of the methods for intraoperative sentinel node identification including Infrared thoracoscopy and radionabelling [6,7]. We will ask whether the investment in technology and time is beneficial for the patient. Is the added information about metastases of clinical value? We will evaluate the argument between nodal sampling vs systematic nodal dissection in non-small cell lung cancer (NSCLC) and attempt to formulate an intraoperative mapping algorithm. Intraoperative nodal mapping has been proposed as a prerequisite to direct the extent of lung resection. We will examine how the findings of nodal disease have been used to discriminate between lobectomy vs pneumonectomy or between lobectomy vs segmentectomy. We will consider the potential role of nodal dissection for more extensive sacrifice of functioning lung tissue. Is there any role for intraoperative nodal analysis in determining the extent of resection? How reliable is this method of nodal mapping? 3. Postoperative Once the pathologist has the resected lymph nodes we will attempt to rationalize how they should be analysed, asking the question: “What are the minimum sampling requirements?”. We will also analyse whether the more detailed nodal mapping of micrometastatic disease by immunohistochemistry significantly influences patient management or outcome [10]. Finally we will discuss how these pathological results could influence the use of adjuvant chemotherapy/ radiotherapy or more interestingly targeted therapies. We discuss how these pathological results could influence the use of adjuvant chemotherapy/ radiotherapy or more interestingly targeted therapies. We consider the argument that nodal metastatic disease is not a justification of clinical value? We will evaluate the argument between nodal sampling vs sentinel node identification including Near Infrared thoracoscopy and radionabelling [6,7]. We will discuss how they should be analysed, asking the question: “What are the minimum sampling requirements?”. We will also analyse whether the more detailed nodal mapping of micrometastatic disease by immunohistochemistry significantly influences patient management or outcome [10]. Finally we will discuss how these pathological results could influence the use of adjuvant chemotherapy/ radiotherapy or more interestingly targeted therapies.
recommended for tumors expressing P790M (Jänne, 2015). In tumors bearing ALK-Ros-gene rearrangements cetiribin is approved and recommended in case of crizotinib resistance (Shaw, 2014). Conclusion: During the past ten years the complexity of the treatment algorithm of advanced NSCLC has gradually increased by the incorporation of several approved molecules. Novel immunotherapies have recently changed the management of advanced wild-type NSCLC. Treatment by histotype and genotype has been established and it can be assumed by the given speed of growth of molecular information that the process of treatment differentiation will fast continue. Identification of new prognostic, and predictive factors undoubtedly will accelerate this process.

SESSION MTE17: MAINTENANCE THERAPY VERSUS EARLY SECOND-LINE THERAPY IN ADVANCED NSCLC (TICKETED SESSION) TUESDAY, DECEMBER 6, 2016 - 07:30-08:30

MTE17.02 MAINTENANCE THERAPY VERSUS EARLY SECOND-LINE THERAPY IN ADVANCED NSCLC
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Several trials have evaluated the appropriate initial duration of platinum based chemotherapy. 3 versus 6 cycles, 4 versus continuous cycles, or 2 versus 4 cycles after non-progression to the initial 2 treatments. In all situations there was no benefit to longer duration of chemotherapy and both ASCO and NCCN recommend no more than 6 cycles of initial treatment. Continuation of lower intensity therapy (typically with a single agent from the initial doublet) was tested after carboplatin-paclitaxel. (Belani et al) or gemcitabine after cisplatin-gemcitabine (Brodzowicz et al) showed no OS difference, but a possible benefit in PFS. Studies evaluated the introduction of a non-cross resistant agent (early second line) in patients without progression after initial chemotherapy. Westett et al. randomized patients after MIB 3 to either observation vs vinorelbine; Fidias et al. evaluated immediate versus delayed docetaxel after carboplatin-gemcitabine x 4 and JMEM study looked into pemetrexed versus paclitaxel after four cycles of platinum doublet. For the latter two studies, about 50% of patients completed 6 maintenance cycles and 50-60% of patients in the observation arm received second line therapy; this is consistent with rates of second line therapy in multiple studies of NSCLC. Results showed a 2.3 month difference in PFS favoring immediate therapy. In terms of overall survival, there was no difference with vinorelbine, and a 2.6-2.8 month difference with either docetaxel or pemetrexed (significant only with pemetrexed). QoL was not affected by continuous chemotherapy and tumor related symptoms improved with pemetrexed. Erlotinib has been evaluated in 3 randomized trials against placebo (SATURN), observation (IFTG-GFPC 0502) or in combination with bevacizumab against placebo-bevacizumab (ATLAS). In all studies there was a PFS benefit (HR 0.71; 0.86), but OS was only significant in the SATURN trial (HR 0.81). PFS benefit was limited to non-squamous histology for pemetrexed, as opposed to the docetaxel and erlotinib trials. Despite the initial negative trials, continuation pemetrexed following platinum-pemetrexed doublet has emerged as a standard option for non-squamous histology. A phase III trial of carboplatin-paclitaxel with or without concomitant and maintenance ipilimumab (an anti-CTLA4 agent) is ongoing, and was initiated taking into account the positive results obtained adding maintenance ipilimumab to the platinum doublet in a previous phase II study. Vaccine therapy has also been studied in 2 settings. The Belagempumatucel-L (Lucainix) is an allogeneic vaccine cancer, obtained from TGF-beta2 anti-sense gene modified whole NSCLC cell lines. There was no difference in overall survival between arms (median survival 20.3 versus 17.8 months with belagempumatucel-L versus placebo, respectively. Tecemotocl (BP-3P) is a vaccine against HPV. START 2 randomized patients with stage III NSCLC who completed chemotherapy with gemcitabine and in SATURN for sequential erlotinib. The ABOUND study with carboplatin-paclitaxel was exploring the role of continuing bevacizumab in combination with a second line chemotherapy, beyond progression to maintenance bevacizumab. In a phase II placebo-controlled study, carboplatin and paclitaxel were given with or without concurrent and maintenance sorafenib, but no improvement in overall survival was shown and the results were detrimental in patients with squamous cell histology. CALGB 30067 of maintenance sumitumib versus placebo met its primary end point of improving PFS (HR 0.78) in favor of continuation maintenance. In pre-specified analysis of patients going through an incomplete cycle of chemotherapy, a 2.9 month difference with vinorelbine, and a 2.6-2.8 month difference with either docetaxel or pemetrexed (significant only with pemetrexed). Despite the initial negative results adding maintenance bevacizumab, there was no OS benefit in an underpowered study. Bevacizumab was also tested. Studies of weekly paclitaxel after carboplatin-paclitaxel were given with or without concurrent and maintenance sorafenib, but no improvement in overall survival was shown and the results were detrimental in patients with squamous cell histology. There was also no effect on OS. EORTC 08092 evaluated pazopanib given as maintenance treatment following standard first line platinum-based chemotherapy in patients with advanced NSCLC. This study was stopped due to lack of efficacy by stringent criteria for PFS at a futility interim analysis. There was no difference in overall survival with the administration of bevacizumab after chemoradiotherapy was found - median OS was 25.6 months with bevacizumab versus 22.3 months with placebo. References 1. Cost-utility analysis of maintenance therapy with gemcitabine and in SATURN for sequential erlotinib. The ABOUND study with carboplatin-paclitaxel was exploring the role of continuing bevacizumab in combination with a second line chemotherapy, beyond progression to maintenance bevacizumab. In a phase II placebo-controlled study, carboplatin and paclitaxel were given with or without concurrent and maintenance sorafenib, but no improvement in overall survival was shown and the results were detrimental in patients with squamous cell histology. CALGB 30067 of maintenance sumitumib versus placebo met its primary end point of improving PFS (HR 0.78) in favor of continuation maintenance. In pre-specified analysis of patients going through an incomplete cycle of chemotherapy, a 2.9 month difference with vinorelbine, and a 2.6-2.8 month difference with either docetaxel or pemetrexed (significant only with pemetrexed). Despite the initial negative results adding maintenance bevacizumab, there was no OS benefit in an underpowered study. Bevacizumab was also tested. Studies of weekly paclitaxel after carboplatin-paclitaxel were given with or without concurrent and maintenance sorafenib, but no improvement in overall survival was shown and the results were detrimental in patients with squamous cell histology. There was also no effect on OS. EORTC 08092 evaluated pazopanib given as maintenance treatment following standard first line platinum-based chemotherapy in patients with advanced NSCLC. 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Peterson, Karen A. Obasaju, Eduardo J. Pennella, Robert K. Chemist, Philip Bonomi, and Ramsawamy Govindan. JCO 31:4349, 2013

Keywords: Maintenance chemotherapy

SESSION MTE18: PERSPECTIVES IN THE SYSTEMIC TREATMENT OF SMALL-CELL LUNG CANCER (TICKETED SESSION) TUESDAY, DECEMBER 6, 2016 - 07:30-08:30
Abstracts
MTE18.01 PERSPECTIVES IN THE SYSTEMIC TREATMENT OF SMALLCELL LUNG CANCER
Mary O’Brien
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Small cell lung cancer is the prototype of a smokers cancer and therefore with
changing smoking patterns and decreasing prevalence of smoking this is a
tumour that happily we are seeing less frequently. However the nature of
the disease, the morbidity and suffering it causes, and the tantalising chemo
and radiotherapy sensitivity of this tumour make it of great medical and
academic interest to us. More attention is now given to the morphology of
small cell lung cancer and the blurred boundary with large cell neuroendocrine
tumours and non small cell lung cancer with neuroendocrine features. At the
end of the EGFR mutation driven lung cancer natural history, small cell lung
cancer appears once resistant has developed to EGFR mutation therapies.
If we start from the early stage disease and look at radical approaches and
how these have changed in the last 20 years we see that the gains made by
systemic treatment have been stable while outcomes have been improved
by intensive local and focused treatments in the form of prophylactic cranial
irradiation and consolidation radiotherapy to the mediastinum. Small gains
have also been made by the timing of radiotherapy both quickly after last
chemotherapy or when given in a concurrent fashion. The Convert study
has now given us a faster twice a day delivery with equal effectiveness and
toxicity to a higher dose once daily schedule. Surgery has never really taken
off as a widely used treatment for SCLC. For all the anecdotal cases who
have been cured with combined treatment involving surgery, we will also
remember those patients who have failed to recover or have delayed recovery
from surgery and lost the window of opportunity for systemic treatment in
a disease that can rapidly change from asymptomatic to very symptomatic.
Despite little change in systemic therapies, it is important that what we
have, we use well and to this end patients with SCLC should be carefully
monitored during treatment for treatment induced neutropenia as this is
readily treated and prevented by the use of GCSF which has become cheap and
readily available in most countries. In addition SCLC was also one of the solid
tumours that benefited from denosumab in the trials of patients with bone
metastases and thus denosumab or zometa should be added to patients with
SCLC who have bone metastases to decrease bone morbidity. Extensive stage
small cell lung cancer is still a challenge and currently a graveyard for drugs
development. The drugs that are looking promising are the PD-L1 inhibitors,
although PD-L1 in itself does not appear to be a biomarker. Anti- PD1 and PD-L1
antibodies, while active in some cases of SCLC are not as broadly active as in
NSCLC. Indeed it does not appear that PD-L1 expression on tumour cells is
not a predictors of response. On could argue that the patients with SCLC who
have a response to anti PD1 therapies may have heterogeneous disease and
have areas of NSCLC which drive the response. It has always been thought
that SCLC must be a problem of proliferation of abnormalities at the stem cell
level. Indeed now it is no surprise that an anti DDL3 antibody (rovalpituzumab
tesirine) is showing activity in relapsed disease – a situation where responses
are few but results of trials are rapid. It also appears that DDL3 expression is
a biomarker to predict response. Once again this biological pathway like the
PD1 pathway, is unpatentable and thus we can expect a florry of antibodies
targeting in and around these receptors on stem cells. The PARP inhibitors
are again a group of drugs that held much promise but as yet have failed to
deliver a treatment option at any point in the SCLC pathway. Further trials are
ongoing. Positive benefits from radiotherapy in extensive stage as in limited
SCLC, tells us that any treatment that can control a site of disease and can
improve outcome, and suggests that removal of clones is important as either
a form of debulking treatment or indeed these clones are a future source of
resistance. Thus research on the treatment of oligometastatic sites either at
presentation, residual after treatment or on relapse, as in the ongoing work in
NSCLC (e.g the Saron study) may lead to future gains in survival. The biology
of SCLC should be approached in the same way as NSCLC i.e. when disease
relapses, rebiopsies should become the norm with as large a piece of tissue as
possible. SCLC also sheds tumour cells into the circulation, which are a source
of material for interrogation. Despite the negative trials, it is still rewarding to
treat SCLC patients – for the rapid improvement in symptoms with treatment
and the small but real group who get long term responses, in addition the
rapid results makes this still an area for many more years of research.
Keywords: small cell lung cancer, heterogenous, neuroendocrine,
chemosensitive

SESSION MTE19: MONITORING OF TREATMENT OUTCOME
IN CLINICAL TRIALS AND IN ROUTINE PRACTICE
(TICKETED SESSION)
TUESDAY, DECEMBER 6, 2016 - 07:30-08:30
MTE19.02 MONITORING OF TREATMENT OUTCOME IN CLINICAL

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TRIALS AND IN ROUTINE PRACTICE
Dimitra Grapsa, Kostas Syrigos
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Monitoring of treatment efficacy and treatment-related toxicity –both
in the real-world and the clinical trial setting- is a crucial, complex and
constantly evolving aspect in the field of modern personalized oncology.
The expansion of our lung cancer armamentarium, due to continuous
implementation of novel (and costly) targeted and immunotherapeutic
agents, along with their companion diagnostics, has inevitably led not only
to substantial improvements in clinical outcomes, but also to increasing
demands for a more accurate prediction and prevention of toxicities and
more robust evaluation of cost-effectiveness. Furthermore, transition to
targeted therapies displaying modes of action and biologic behavior vastly
distinct to those of traditional cytotoxic agents, has necessitated the need
to revisit our concept of what constitutes “tumor response” in lung cancer
treatment (and solid tumors in general). Vital issues that need to be urgently
-albeit concertedly- addressed include –but are not limited to- the need to
adapt response evaluation criteria, monitoring tools and techniques to this
rapidly changing landscape of lung cancer treatment and to increase our focus
towards a patient-centered standard of care. Monitoring of treatment efficacy
using imaging modalities Monitoring of tumor size changes -as evidenced
on quantitative imaging modalities such as CT and MRI scans and typically
assessed by the unidimensional RECIST criteria- remains the cornerstone of
treatment response evaluation and decision-making in oncology practice and
a strong surrogate endpoint for overall survival in clinical trials. Limitations
of this approach are, nevertheless, significant and increasingly recognized.
First, measurement inaccuracies and considerable inter-observer variability
should be pointed out. Second, considerable time and cycles of cytotoxic
drugs are needed prior to the appearance of any clinically meaningful tumor
size changes on standard imaging studies, meaning that a reduction of tumor
volume alone may not represent an early indicator of treatment response.
Third, antitumor activity of targeted agents, which may not necessarily
result in significant tumor size modification, cannot be accurately assessed
or predicted with the use of these conventional strategies; multiparametric
imaging –evaluating both anatomical and functional parameters of tumorsis thus required for optimal assessment of tumor behavior (stability,
progression or regression). Within this context, functional imaging modalities
(i.e. dynamic contrast-enhanced MRI, diffusion weighted imaging or FDGPET and FLT-PET ) with the potential to visualize physiologic changes in
the molecular level, have been investigated for their ability to influence
decision-making by predicting or monitoring response to molecularly targeted
agents or their value as surrogate outcome measures in the trial setting.
Notably, FDG-PET is increasingly used for the evaluation of treatment
response (mainly with PET response criteria /PERCIST) in lung cancer, while
it is generally acknowledged that combined use of both RESIST and PERSIST
criteria might lead to increased accuracy of prediction of treatment response
in the earlier treatment stages. Evidently, earlier recognition of tolerance to
treatment is vital for reduction of unnecessary toxicity and increase of costeffectiveness. The barriers of complexity, high cost and limited availability,
with regard to the above functional imaging techniques, should nevertheless
also be emphasized. Evaluation of response to immune checkpoint inhibitors
represents an emerging challenge in the field of immuno-oncology; since the
specific patterns of tumor response to these agents cannot be accurately
described using conventional imaging criteria, immune-related response
criteria (irRC) were first defined in 2009, so as to provide a “common
language”, enabling the application of a unified assessment of response
to immunotherapy. Controversy with regard to the use of bidimensional
measurements (according to the WHO criteria) in the irRC nevertheless
ensued; immune-related RECIST 1.1 criteria are now increasingly used in clinical
studies. Immune-related response evaluation remains to be implemented
in routine practice and seems to represent an emerging endpoint in clinical
trials. Monitoring of treatment efficacy using non-imaging modalities
Monitoring of response to biomarker-driven therapies targeting specific
molecular alterations in the lung cancer genome remains a major challenge
in the field of personalized oncology, mainly due to shortage of tissue for
the performance of genetic profiling of tumors. Liquid biopsies –detecting
circulating tumor cells/CTCs and fragments of cell-free circulating tumor
DNA/ctDNA- carry much promise for becoming an excellent and non-invasive
alternative to tissue-based testing for the identification of genetic mutations
with prognostic or therapeutic relevance. As a blood-based biomarker,
ctDNA analysis offers the potential of serial investigations at any time point
during the course of treatment, and thus of real-time dynamic monitoring
of treatment response and early identification of acquired resistance to
treatment or even early detection of recurrence (ideally prior to visible tumor
size changes on imaging). The first liquid biopsy test approved by the FDA as
a companion diagnostic, cobas® EGFR Mutation Test v2, is now increasingly
used in routine practice for EGFR mutation testing in patients with advanced
non-small cell lung cancer, expanding the access of this population to
potential disease-modifying treatments. Comprehensive molecular profiling
of tumors using next-generation sequencing (NGS) analysis of ctDNA is
another major advancement in personalized lung cancer oncology, with
tremendous potential for monitoring of dynamic tumor behavior in response

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SESSION MTE21: NEXT GENERATION SEQUENCING (TIKTED SESSION)
WEDNESDAY, DECEMBER 7, 2016 - 07:30-08:30

MTE21.01 NEXT GENERATION SEQUENCING
Ignacio Wistuba1, Xuefei Li2
1Translational Molecular Pathology, The University of Texas MD Anderson Cancer Center, Houston/United States of America, 2Medical Oncology, Shanghai Pulmonary Hospital, Shanghai/China

Non small cell lung cancer (NSCLC) with sensitive epidermal growth factor receptor (EGFR) mutations invariably develop resistance to EGFR tyrosine kinase inhibitors (TKIs). 20%-30% of NSCLC patients harboring sensitive mutations have no initial clinical response to EGFR-TKIs, which is defined as having intrinsic resistance to EGFR-TKIs; while the rest of patients activating mutations who are initially responsive to EGFR-TKIs eventually developed acquired resistance after 10–12 months of consistent clinical benefit, followed by disease progression. The drug resistance is a really tough and urgent clinical problem. Part of resistant mechanisms have been reported, including BIM deletion polymorphism, combined with other bypass signal pathway activation, epithelial-mesenchymal transition (EMT) for primary resistance; T790M, cMET amplification, SCLC transformation for acquired resistance. However, partial resistant mechanisms still unknown. In contrast to acquired resistance to EGFR-TKIs, intrinsic resistance is more complicated. Next-generation sequencing (NGS) is a promising tool for analysis of tumor mutations. We aimed to investigate the intrinsic resistant mechanisms to EGFR-TKIs by NGS, further to optimize treatment strategies and improve clinical outcome in EGFR activating mutant patients having intrinsic resistance to EGFR-TKIs. At present, the study is underway, and the results will be presented at the 2016 WCLC.

Keywords: next-generation sequencing, NSCLC, EGFR-TKIs, drug resistance assessment

SESSION MTE22: PERSPECTIVES IN LUNG CANCER IMAGING (TICKETED SESSION)
WEDNESDAY, DECEMBER 7, 2016 - 07:30-08:30

MTE22.01 PERSPECTIVES IN LUNG CANCER IMAGING
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Lung cancer is still the leading cause of cancer-related death in both men and women with 80% to 85% of cases being non-small-cell lung cancer (NSCLC). Over the past years, the IASLC Staging and Prognostic Factors Committee has collected a new database of 94,708 cases of lung cancer as the backbone for the upcoming 8th edition of the TNM classification for lung cancer due to be published late 2016 1. The 8th edition will significantly impact lung cancer staging with CT and PET-CT due to the subclassification of T1 and T2 into a, b, and c categories, the reclassification of tumors more than 5 cm but not more than 7 cm in greatest dimension as T3, the reclassification of tumors more than 7 cm in greatest dimension as T4, the grouping of the involvement of the main bronchus as a T2 descriptor, regardless of distance from the carina, but without involvement of the carina, the involvement of the carina, total atelectasis or pneumonitis as a T3 descriptor, the reclassification of diaphragm invasion as T4 and the exclusion of mediastinal pleura invasion as a T1 descriptor 1,2. Moreover, the upcoming 8th edition will also lead to a novel classification of distant metastasis, in which single extrathoracic metastasis will be classified as M1b whereas in multiple extrathoracic metastasis will be classified as M1c. The changes made within the proposal of the 8th edition of the TNM will be discussed within the presentation using clinical examples. Beside the accurate staging of patients with lung cancer early detection using CT screening with novel low radiation dose CT technologies will also be discussed. Within this context, a special focus will be given on novel methods that may improve a more accurate characterization of detected lung nodules using deep machine learning and Radiomics. Radiomics refers to the comprehensive quantification of lung nodule and tumour phenotypes by publishing a large number of morphological features that are standardized collected with specific software algorithms. Radiomics features have the capability to further enhance imaging data regarding prognostic tumour signatures, detection of tumour heterogeneity as well as the detection of underlying gene expression patterns which is of special interest in patients with lung cancer. Signalling pathways and genetic driver mutations that are vital for tumour growth have been identified and can be effectively targeted by molecular,pathologically interacting in significant that patients with lung cancer. Parallel to the progress in lung cancer treatment, imaging techniques aiming at improving diagnosis, staging, response evaluation, and detection of tumour recurrence have also considerably advanced in recent years. However, standard morphologic computed tomography (CT) and magnetic resonance imaging (MRI) as well as fluorodeoxyglucose (18F-FDG) positron emission tomography CT (PET-CT) are still the currently most frequently utilized imaging modalities in clinical practice and most clinical trials 1,2. Novel state-of-the-art functional imaging techniques such as dual-energy CT (DECT), dynamic contrast-enhanced CT (DCE-CT), diffusion weighted MRI (DW-MRI), perfusion MRI, and PET-CT with more specific tracers that visualize angiogenesis, tumour oxygenation or tumour cell proliferation have not yet been broadly implemented, neither in clinical practice nor in phase I-III clinical trials. In this context, Nishino et al. published an article on personalized tumour responses in NSCLC patients with lung cancer. As the development in tumour response assessment that should parallel the developments in tumour response assessment may not reliably indicate treatment failure and do not adequately capture disease biology. Molecular-targeted therapies and novel immunotherapies induce effects that differ from those induced by classic cytotoxic treatment including intratumoral haemorrhage, changes in vascularity, and tumour cavitation. Thus, conventional approaches for therapy response assessment such as RECIST or WHO criteria that exclusively focus on the change in tumour size are of decreasing value for drug response assessment in clinical trials 3,4. In summary, the aim of this presentation is to provide an overview on the changes made within the upcoming 8th edition of the TNM classification as well as to provide an overview on state-of-the-art imaging techniques for lung cancer screening, staging, response evaluation as well as surveillance in patients with lung cancer. The various techniques will be discussed regarding their pros and cons to further provide functional information that best reflects specific targeted therapies including anti-angiogenetic treatment, immunotherapies and stereotactic body radiation therapy.

Abstracts

SESSION MTE24: IMMUNOHISTOCHEMICAL ASSESSMENT OF BIOMARKERS FOR IMMUNE CHECKPOINT INHIBITORS (TICKETED SESSION)
WEDNESDAY, DECEMBER 7, 2016 - 07:30-08:30

MTE24.01 IMMUNOHISTOCHEMICAL ASSESSMENT OF BIOMARKERS FOR IMMUNE CHECKPOINT INHIBITORS
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Immune checkpoint inhibitors in cancer immunotherapy. Programmed death receptor-1 (PD-1) is a type 1 membrane protein of the immunoglobulin superfamily that has an important role in restricting immune-mediated tissue damage secondary to inflammation and/or infection (1). The clinical advantages of these therapies have been used to block this ligand-receptor interface, allowing cancer killing by T cells became clear when CTLA4, an antagonist against the T-cell, such as ipilimumab, and afterward PD-1, showed an increase survival in patients with metastatic melanoma (2). Clinical investigations in lung cancer have demonstrated the benefit of PD-1 inhibitors pembrolizumab in advanced non-small cell lung cancer (NSCLC) and nivolumab in advanced squamous and nonsquamous NSCLC; both approved as second-line therapies by the US Food and Drug Administration (FDA) (3-5). Others PD-L1 inhibitors such as atezolizumab and durvalumab have demonstrated effectiveness in several tumor types (6-7) but they were not approved for clinical use until now. PD-L1 inhibitors induce around of 20% of complete response frequency in patients with NSCLC, and persistent response in a subgroup of patients treated by immune checkpoint inhibitors. Garon et al (3) showed that tumors with PD-L1 expression ≥ 50% by immunohistochemistry (IHC) were significantly more expected to respond to pembrolizumab than those with less than 50% malignant cell expression. In contrast, response rates to nivolumab are significantly more expected to respond by immunohistochemistry (IHC) with PD-L1 positivity in both tumor and immune cells were seen in only 9% of patients. They found that 20% of lung tumors cell expressed PD-L1 (≥ 20% intensity 2+≥3), and 29% the immune stromal cells (T, macrophages, DC) ≥10% intensity 2+≥3. PD-L1 positivity in both tumor and immune cells were seen in only 9% of NSCLC, 20.7% were both negative. There was no prognostic relevance of PD-L1 (tumor cells or stroma) whatever cut off by 10% increment or linear scoring was used. Only immune PD-L1 expression was correlated with a highly intense immune infiltrations. Previous published evaluations of prognostic value were discordant likely because immune checkpoints modulators play both positive and negative roles in the immune inhibitory pathways with some redundancy, and patients series and assays were not comparable. The two meta-analyses with different antibodies, cutoffs, patient series, ethnicities and contribution of oncogene driven cancers, initial resection sample or contemporary biopsy rendered their interpretation extremely problematic. Global result was supporting a poor prognosis of “PD-L1 positivity” on tumor cells.

PD-L1 as a Predictive Biomarker for Checkpoint Inhibitors. Most of phase I trials works with four antibodies targeting PD-1 or its primary ligand PD-L1, response rates appear higher in patients with increased tumor PD-L1 membrane expression by IHC. However, different antibody assays, absence of standardization, different score to determine PD-L1 positivity, companion test type, and a short number of specimens available for testing, accrued to the variability of the intervals between biopsy and test, has certainly disadvantaged the conclusion and prevent consensus to be reached (10). The best threshold was provided by Garon et al, with ≥50% of tumor cells PP-L1 positive to allow the highest response rate of 45% to pembrolizumab (3). In most trial series, biopsies or resected specimen were used and considerable difference between these samples occurs due to tumor heterogeneity. The reliability of small biopsy samples is questioned (10). Indeed lung tumor heterogeneity is characteristic and PD-L1 is typically heterogeneous in its distribution in the tumor majority as is PD-L1 positive immune cells. Multiple questions still are addressed before PD-L1 is considered as a definitive molecular predictor of effectiveness. As for prognostic evaluations, thresholds of ≥1%, ≥5%, ≥10%, ≥50% or continuous H score have been used. In addition, in a few trials, PD-L1 expression in TILs was predictive more than PD-L1 on tumor cells but the best cut off was not revealed.

Conclusion. PD-L1 expression predicts response to immune checkpoint inhibitors. Concordant results showing a better response if PD-L1+ in several trials, using drug specific test and for Nivolumab also histology specific. We should evaluate membranous staining in tumor sample with at least 100 tumors cells and immune cells. Perspective for upgrading includes: 1) heterogeneity of the expression of PD-L1 within tumor, primitive vs metastases number and size of samples; 2) surgical tissue versus biopsy and 3) archival versus new biopsy and 4) standardize the assays. Published abstracts showed high rates of concordance between primary and metastases (81%). Obtaining different biopsies from different areas of the same tumor would enhance the validity of the results of IHC evaluation (160 patients=48% discordance).

References
SESSION MTE26: EGFR TARGETED THERAPIES: LESSONS LEARNED
WEDNESDAY, DECEMBER 7, 2016 - 07:30-08:30

MTE26.02 EGFR TARGETED THERAPIES: LESSONS LEARNED
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Abstracts
Journal of Thoracic Oncology • Volume 12 Issue S1 January 2017

Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors (EGFR-TKIs) are the standard therapy for patients with Non-Small-Cell Lung Cancer (NSCLC) harboring activating EGFR mutations. During the last 10 years several trials demonstrated that first and second generation EGFR TKIs such as erlotinib, gefitinib or afatinib are superior to standard platinum-based chemotherapy in terms of efficacy and tolerability and quality of life. Development of EGFR-TKIs led to a dramatic change in mentality of physicians treating NSCLC. For many years NSCLC has been treated with chemotherapy and platinum-based doublets were offered to all patients irrespective of biological characteristics. Knowledge in the field of molecular biology were limited and even a small cytological sample was sufficient for defining the therapy. Tumor biopsy was recommended only at the time of initial diagnosis and changes in tumor biology as a consequence of therapy exposure were largely unknown. Discovery of EGFR mutations and the impressive activity observed with EGFR-TKIs in EGFR mutated patients led clinicians to understand the relevance of patient selection based on biomarker assessment and therefore the importance of tumor tissue analysis. Since EGFR-TKI approval, EGFR testing entered onto clinical practice and today several biomarkers are routinely tested in NSCLC patients for defining the best therapeutic strategy. In addition to EGFR, other biomarkers such as ALK or ROS1 rearrangements or PD-L1 expression are guiding physician for therapy choice and additional tests are expected to reach the clinic in the future. As a consequence, tumor biopsy and tissue collection become relevant in clinical practice and also in trial design, since modern studies often claim for tumor tissue. In addition, identification of mechanisms responsible for acquired resistance led to repeat tumor biopsies. Unfortunately, in NSCLC, the amount of tissue obtained at the time of primary diagnosis is often not abundant and tumor re-biopsy if feasible in the minority of patients. Such limitations are leading to development of the so-called “liquid biopsy”, allowing physicians to obtain biomarker information in circulating tumor DNA. In addition, new technologies are implementing the possibility to test for multiple biological events using a single experiment, with a significant reduction in amount of tissue needed, reducing time and costs. Development of EGFR inhibitors also led to a different approach for treating lung cancer. For the first time physicians faced with oligo-progression diseases, consisting in disease slowly progressing under EGFR-TKI therapy. Often the disease remains asymptomatic and it is still partially sensitive to the therapy. The possibility to control disease outcome by continuing the targeted agent led to the concept of “treatment beyond progression”, an approach that is preserving patient quality of life with also a favorable impact on duration of life. Finally, and EGFR therapies are also highlighting the new opportunity for treating brain metastases. Brain metastases (BM) are a frequent complication of NSCLC, with 25–40% of patients developing BM during the course of the disease, often within the first 2 years after the primary tumor diagnosis. A review of 1,127 NSCLC patients found that those with EGFR mutations were more likely to develop BM than those with such mutations. The frequency of BM was thus 31.4% for the mutation-positive patients but only 19.7% for the negative ones. Improvements in neurologic symptoms and performance status have been reported with whole-brain radiation therapy (WBRT) in combination with steroid therapy in these patients. However, due to their poor performance status, many patients with BM are not eligible for surgery or radiosurgery. Furthermore, the role of systemic chemotherapy for the treatment of BM is controversial due to the impenetrable nature of the blood brain barrier (BBB), with reported response rates to chemotherapy ranging from 15–30% (overall survival [OS] 6–8 months). Response rates of brain metastases to EGFR tyrosine kinase inhibitor (TKI) treatment (e.g. gefitinib, erlotinib, afatinib in patients with NSCLC harboring EGFR mutations reach 60–80%, with a complete response rate as high as 40%. Median OS is 15–20 months, and progression-free survival in the brain reaches 6.6–11.7 months, demonstrating improved clinical outcome (Table I). Nevertheless, first and second generation EGFR-TKI may have limited BBB penetration. New EGFR-TKIs including the third-generation EGFR-TKI osimertinib and AZD3759, an oral reversible inhibitor of EGFR activating mutations, recently showed impressive activity in presence of BM. The possibility to obtain a long lasting brain disease control together with the positive impact on duration of life is also impacting on the strategy of BM treatment, with preference for therapies not or modestly impacting on cognitive functions, such as stereotoxic radiotherapy, and a lower usage of WBRT. Reference: 1. Porta R, et al. Eur Respir J 37: 624-631, 2011. 2. BPark SJ, et al. Lung Cancer 77: 556-560, 2012. 3. Li Z. J Clin Oncol 29 (Suppl): abstract e18065, 2011. 4. Kim J, et al. Lung Cancer 65: 351-354, 2009. 5. Welsh JH, et al. J Clin Oncol 31: 895-902, 2013. 6. Luch T, et al. Lung Cancer 82: 282-287, 2013. 7. Hoffknecht P, et al. J Thorac Oncol 10: 156-163, 2015.

Keywords: EGFR, brain metastases

SESSION MTE27: TREATMENT OF LUNG CANCER PATIENTS WITH POOR PERFORMANCE STATUS (TICKETED SESSION)
WEDNESDAY, DECEMBER 7, 2016 - 07:30-08:30

MTE27.01 TREATMENT OF LUNG CANCER PATIENTS WITH POOR PERFORMANCE STATUS
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Performance status (PS) captures a patient’s ability to perform daily activities and provides a measure of impairment as a function of tumor burden. The Eastern Cooperative Oncology Group (ECOG) scale is the most frequently used and ranges from 0 (fully ambulatory without symptoms) to 5 (dead). Typically, patients with an ECOG PS of 0 and 1 are labeled as “good PS”, are typically treated with combination regimens, and are the focus of the majority of the clinical trials. Patients with “poor PS”, mostly ECOG 2, but also 3 and occasionally 4, have been largely excluded from clinical trials. Patients with a PS of 2 account for approximately 30-40% of patients diagnosed with advanced non-small cell lung cancer (NSCLC) in clinical practice (3). As a result of the lack of dedicated research, current guidelines are equivocal with respect to the optimal therapy for these patients and their management remains inconsistent, ranging from best supportive care to combination chemotherapy. Cooperative group studies in the 1980’s and 1990’s suggested that poor PS patients (ECOG ≥2) derived little or no benefit from systemic chemotherapy and had high rates of treatment-related morbidity and mortality (2). This perspective permeated clinical research and clinical practice for over 2 decades. While concerns about safety and benefit remain appropriate, the advent of better supportive care, along with more effective and tolerable carboplatin-based doublets have led to new trials in this subset of patients. Two large phase III randomized trials in PS 2 patients in the mid-2000’s provide insights into this heterogeneous cohort. In one trial, 400 patients were assigned to standard carboplatin plus paclitaxel or carboplatin plus another formulation of paclitaxel (3). In the other trial, 400 patients were assigned to single agent gemcitabine or vinorelbine (4). The identical eligibility criteria led to a separate publication

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Comparing single agent vs. combination chemotherapy (5). The response rate (38% vs 16%) and the median time to progression (4.6 vs 3.5 months) were statistically superior with combination chemotherapy. Overall survival trended in the same direction, but the difference was not significant (8.2 vs 6.6 months). Toxicity, expected, was higher with combination chemotherapy. The question of single agent vs combination chemotherapy was addressed in a definitive manner by a phase III randomized trial that compared pemetrexed alone or in combination with carboplatin in 205 eligible patients with PS 2 (6). Respectively, the response rates were 10% vs 24%; the median progression free survival was 2.8 vs 5.8 months and the median survival was 5.3 vs 9.3 months, all statistically significant in favor of the combination regimen. Toxicity was manageable but 4 treatment-related deaths were observed in the combination arm. This trial has set a new standard for treatment of advanced NSCLC patients with a PS of 2.

The advent of targeted agents led to the exploration of these agents as a “gentler approach” to PS 2 patients, irrespective of the presence or absence of the mutation. In a phase II randomized trial, patients were assigned to either erlotinib or a combination of carboplatin and paclitaxel (7). Patients treated with erlotinib had a significantly shorter median survival compared to chemotherapy (6.5 vs 9.7 months, HR 1.73, 95% CI 1.19-2.73). As shown in other trials, EGFR inhibitors should not be given to untreated patients without the mutation, regardless of the PS. Guidelines from the American Society of Clinical Oncology (ASCO) state that the data for patients with PS 2 are insufficient to make a strong recommendation for combination chemotherapy, and single agent therapy may be appropriate if the perception of risk outweighs the perception of benefits (8). The European Society of Medical Oncology (ESMO), after reviewing the same body of data, came up with a straightforward recommendation for carboplatin-based combinations to all eligible PS 2 patients (9). The National Comprehensive Cancer Network (NCCN) merged PS 2 patients into the PS 0-1 group for recommendations regarding first line therapy, with no obvious distinction between the subsets (10). This progressive approach recognizes the advances made in the management of PS 2 patients in the past decade and extends the benefits of systemic therapy to a large group of patients who were, until recently, offered inferior treatments. References: Lilenbaum RC, Cashy J, Hensing TA, et al. Prevalence of poor performance status in lung cancer patients: implications for research. J Thorac Oncol 2008; 3:125


Keywords: Advanced NSCLC PS 2

SESSION MTE28: IMPLEMENTATION OF PRECISION MEDICINE IN ROUTINE PRACTICE: THE LATIN AMERICAN EXPERIENCE (TICKETED SESSION)
WEDNESDAY, DECEMBER 7, 2016 - 07:30-08:30

MTE28.01 IMPLEMENTATION OF PRECISION MEDICINE IN ROUTINE PRACTICE: THE LATIN AMERICAN EXPERIENCE

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Technology for molecular testing in lung cancer is a highly demanding aspect to tackle in the LATAM countries. Molecular testing requires incorporation of new technologies usually involving expensive equipment, reagents and supplies. Moreover, these items are commonly imported from other countries and are subjected to custom regulation and heavy taxes. Therefore, LATAM labs commonly face delays in the process of purchase orders, are constantly adjusting to changes in regulations and in the country’s financial status, and suffer from slow and sometimes poor support from companies that do not see them as preferred clients. As an example of consequences of some of these points, in Argentina the agents Nivolumab and Pembrolizumab were never approved for immunotherapy for NSCLC before the molecular testing laboratories had conditions to purchase the DAKO platform and the CDx antibodies for appropriate IHC testing. Some technical devices such as automated IHC platforms are more widely available. They were initially integrated onto large pathology labs in the main cities of several countries but smaller automated platforms are currently available in a number of other cities. There are laboratories equipped for fluorescence in situ hybridization (FISH) and for DNA sequencing in most countries. Sanger sequencing is still commonly used, but the main laboratories already incorporated newer technologies such as RT-PCR allele-specific technologies (usually Cobas Assays) and adequate panels of next generation sequencing (NGS) or have them in the short list for implementation. Additionally to the challenges in the laboratories organization, two other main issues obstruct the implementation of lung cancer molecular testing in the LATAM countries: the lack of a stable logistic infrastructure necessary to ship biological samples to large reference laboratories, and the lack of qualified laboratories in a cheap, reliable and rapid way, and the hurdle of cost reimbursement for the tests. In the past 10 years, expenses and logistics for transfer of biological samples and reimbursement for molecular testing costs, in most countries such as Mexico, Brazil, and Argentina, were sponsored by pharmaceutical companies. Companies such as AstraZeneca, Roche, Boehringer Ingehelm, and Pfizer have acted through clinical trials or special access programs. In a smaller scale, molecular tests have been supported by governmental health agencies or covered by private health care insurance companies. The advent of targeted agents led to the exploration of these agents as a new standard for treatment of advanced NSCLC patients with a PS of 2. The National Comprehensive Cancer Network (NCCN) merged PS 2 patients into the PS 0-1 group for recommendations regarding first line therapy, with no obvious distinction between the subsets (10). This progressive approach recognizes the advances made in the management of PS 2 patients in the past decade and extends the benefits of systemic therapy to a large group of patients who were, until recently, offered inferior treatments.

References:


Data from at least 15 of the highest populated LATAM countries regarding their lung cancer test menu, the technical platforms used, and efforts for investigation of the assay performance characteristics have been surveyed and results will be discussed.

**Keywords:** Precision Medicine, Latin America

**MTE28.02 IMPLEMENTATION OF PRECISION MEDICINE IN ROUTINE PRACTICE: THE LATIN AMERICAN EXPERIENCE**

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The increasing application of the concept of precision medicine (PM) in the last decade has revolutionized health care. Under this concept, the approach to disease treatment and prevention takes into account individual variability in genes, environment, and lifestyle to more accurately predict disease and prevention strategies for a particular disease in specific patient subsets. PM has been progressing faster among infectious diseases and neoplasia, with emphasis in non-small cell lung cancer (NSCLC) among the solid tumors. However, we are still far away from a stable scenario to which we should adjust. The latest is the continuous evolution with constant new discoveries and proposals. The implementation of PM for lung cancer has dramatically impacted several medical areas mainly in two basic aspects: the molecular diagnosis and the therapy regimen. The first involves questions such as how to collect and process specimen for testing, which tests to apply and in which order, how to define scoring criteria and cut-offs for variables with continuous distribution in the population, how to interpret and validate clinical assays, and how to properly communicate with the multidisciplinary team. The second involves questions pertinent to understanding the molecular diagnostic criteria and cost of new pharmaceuticals, evaluation of side effects, selection of combination or sequential regimens, definition of clinical progression and resistance, and proper communication with the multidisciplinary team. Our discussion will primarily address molecular testing in lung cancer in Latin America countries (LATAM). One of the medical areas most affected by the changes accompanying PM in medicine is the pathology. The new specialty of Molecular Pathology has emerged to focus on the sub-microscopic aspects of disease by examination of molecules within tissues and bodily fluids. Molecular Pathology encompasses aspects of anatomical and clinical pathology as well as molecular biology, biochemistry, genomics, and informatics. Molecular pathology testing in Latin America is centralized in the main cities of several countries and usually performed in laboratories of few, large, private markets, mostly belonging to academic institutions. Examples of those laboratories are located in the Hospital Italiano and Hospital Roffo in Buenos Aires, Argentina; in the Instituto Nacional de Cancerología in Mexico City; in the Institut de Cancerología in Sao Paulo, Brazil; in the Universidad Católica de Chile; in the Fundación Hospital Italiano and Hospital Roffo in Buenos Aires, Argentina; in the Instituto Nacional de Cancerología in Mexico City. There are also few commercial laboratories that offer standard tests under good laboratory practices. Examples are the laboratories Hermes Pardini and Consultoria em Patologia in Brazil, Argenomics and Biomarkers in Argentina, and ROE in Peru. The implementation of molecular testing poses some important challenges to pathology practices in commercial and academic institutions, and efforts to overcome them have been extensively discussed. It is well recognized that changes in two organizational levels are required, one related to personnel and another related to equipment and technology. In terms of personnel, there is a need to increase multi-disciplinary communication affecting all areas including oncologists or surgeons requesting the tests, professionals (surgeons, pathologists) collecting the specimen, the technologists processing and handling the specimens, pathologists performing histology diagnosis and molecular testing interpretation, lab scientists (biologists, biotechnologists, biochemists) executing assays and interpreting the results, and bioinformaticians handling computer-generated data. The interdisciplinary work in the anatomic and clinical pathology laboratory must be intensified and personnel with distinct expertise and no clinical experience must be added and integrated to the team. The role of the pathologist in the communication and integration among team members (clinical/medical and laboratory group) is crucial. Interestingly, the work environment in a complex molecular testing laboratory has changed to demand personnel not only with excellent hard technical skills but also with soft skills such as active listening, coordination, adaptability, punctuality, problem solving, and friendly personality. The lab success relies in that each team member clearly understands his/her role and the value of efficient communication among team members. To overcome these challenges, most of the LATAM laboratories already performing molecular testing have increased and strengthened this interdisciplinary work using biologists and biotechnologists originally trained in research fields.

Nevertheless, the continuous update with the evolving field required from the pathologists, the scarceness of trained bioinformaticians for data sequencing analysis, and the vigorous integration of the entire professional team are still challenging personnel issues to be addressed. Data from at least 15 of the highest populated LATAM countries regarding their efforts in initiating and expanding molecular testing for lung cancer and the strengths and challenges faced have been surveyed and results will be discussed.

**Keywords:** Pathology, Latin America, molecular testing

**SESSION MTE29: ADVANCES IN MALIGNANT PLEURAL MALIGNANCY**

**MTE29.01 ADVANCES IN MALIGNANT PLEURAL MESOTHELIOMA**

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**Background**

More than 30 years have passed since industrialized countries started to strictly regulate the use of asbestos, including, in several of them, introducing a total ban on import of raw material and of asbestos-containing products. The use of the International Classification of Diseases (ICD) to classify deaths from mesothelioma has been a source of concern in the past because, before the 10th version of ICD (ICD-10), no specific code existed for this type of neoplasm, and analyses based on entities such as ‘pleural cancer’ were subject to misclassification. Since the late 1990s ICD-10 has been used for death certification in many developed countries. **Methods** We analyzed age-specific mesothelioma mortality rates (all sites), calculated on the basis of the data of the WHO Mortality Database, among men from Canada (2000-2011), USA (1999-2013), Japan (1995-2008), France (2000-2011), Germany (1998-2013), Italy (2003-2012), the Netherlands (1996-2013), Poland (1999-2013), United Kingdom (2001-2013) and Australia (1998-2011), based on ICD-10, to identify temporal patterns following reductio of asbestos exposure. Results Mortality in the age groups 35-54 and 55-64 decreased throughout the study period in all countries (median decrease, 7.9% per year and 4.1% per year, respectively) except in Poland and (up to 2007) in Japan, two countries which started from lower rates. In the age group 65-74, mortality decreased in the USA and, since 2009, in the Netherlands, was stable in Australia, and increased in other countries (median increase, 3.0% per year). In the age group above age 74, a decrease was apparent only in the USA after 2003 (median increase in the other countries, 3.5% per year). **Conclusions** Our analysis, based on consistent mortality data for mesothelioma, provide strong evidence for a decrease in mortality in the young age groups in most high-income countries: these birth cohorts experienced reduced opportunity for exposure to asbestos during their occupational life. In the case of older age groups, whose members had greater opportunity of exposure, in particular to amphiboles, the evidence of a decrease in mortality is present only in a few countries. Overall, these results stress the importance of early-life exposure circumstances to determine mesothelioma risk throughout life.

**Keywords:** Mesothelioma, epidemiology

**MTE29.02 ADVANCES IN MALIGNANT PLEURAL MESOTHELIOMA**

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**Epidemiology:** MPM, representing around 90% of all mesothelioma cases diagnosed, is an aggressive tumour with a poor prognosis, and relatively few treatment options. The association of mesothelioma with asbestos exposure is well established. The latency period, the interval between first asbestos exposure to the diagnosis is long (around 40 years), and explains why in many instances the effect of banning asbestos from the workplace has yet to be seen. At the same time there is evidence accumulating that non-occupational asbestos exposure may significantly contribute to mesothelioma incidence [1] and it is most worrying that unrestricted use of this carcinogen is allowed in Russia and most Asian, African and South American countries. Unfortunately the multilateral treaty to promote shared responsibilities in relation to hazardous chemicals (Rotterdam convention) has become paralyzed by the veto of asbestos producers and considering the rapid surge of asbestos consumption in developing countries the end of the mesothelioma epidemic is not in sight [2]. Molecular biology: Major efforts have been undertaken to

**Keywords:** Mesothelioma, epidemiology

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**Abstracts**

**MTE28: IMPLEMENTATION OF PRECISION MEDICINE IN ROUTINE PRACTICE: THE LATIN AMERICAN EXPERIENCE**

**Wednesday, December 7, 2016 - 07:30-08:30**
Abstracts

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explore the genomic alterations responsible for the development of malignant pleural mesothelioma. Recent next-generation sequencing efforts have confirmed the frequent loss of tumour suppressor genes identified in earlier studies. Deletions and loss of function mutation of CDKN2A, NF2, and BAP1 are common molecular events in MPM, but the overall mutational load tends to be lower in MPM than in lung cancer. Mutation, aberrant splicing, and gene fusions occur in additional genes such as SF3B1, TRAF7 and SETD2, but at lower frequency [3]. Expression analyses suggest that there are subgroups of tumours based on the traditional histopathological subtypes of MPM [3, 4], and this has potential implication for prognosis. Although still to be published, the results from a TCGA mesothelioma study paint a similar picture of the mutational and transcriptional landscape. Investigation of microRNA expression reveals a general downregulation of microRNAs with tumour suppressor activity. In addition to miR-31, frequently co-deleted with CDKN2A, the miR-15/16 family is consistently downregulated in MPM tumours. This family controls expression of targets such as Bcl-2, CCND1 and VEGF, and thus plays a role in the regulation of proliferation, apoptosis and angiogenesis. Recent data suggest that these microRNAs also play a role in controlling the levels of PD-L1 expression in MPM cells [5], targeted by immune checkpoint inhibitors. Treatment Options: MPM is notoriously refractory to localized and systemic treatment. Meta-analyses (multivariate analyses) of large series of patients confirm that the prognosis of the select group of patients able to undergo radical surgery is significantly better than without surgery [6] despite the fact that this subgroup has not been shown to receive benefit over placebo in 2 major step forward. However, monotherapy with Tremelimumab, inhibitor of immune checkpoint (PD-L1) inhibition [12] seem to indicate that reversing the immunogenic tumour type and the preliminary data showing responses after activity in pre-treated MPM patients [11]. It has become clear that MPM is an the inhibitor of the NF2/mTOR/FAK pathway, have also failed to show notable III studies including bortezomib, vorinostat, everolimus, and defactinib, a range of inhibitors of growth factors including EGFR, VEGF and PDGF had note that a not insignificant number of negative phase II and III studies with a new therapy standard. Thirteen years later this standard has been augmented by a large comparative French intergroup study revealing that the addition of consolidation radiotherapy after radical surgery [7] has not been shown to provide major benefits in terms of local control. To define the role of (intensity modulated) accelerated radiotherapy in MPM comparative studies are needed. The impressive data (median overall survival of 51 months) from the SMART study [8] combining pre-operative intensity modulated radiation therapy (IMRT) immediately followed by extra-pleural pneumonectomy in 62 patients MPM patients with epithelial histology suggests that such an approach may have the potential to become an alternative for induction chemotherapy followed by radical surgery. Almost every chemotherapy agent has been tested in MPM. Cisplatin, metotrexate, pemetrexed and the anthracyclines doxorubicin and daunorubicin were most active, but single agent activity seldom exceeded a 20% response rate. A systematic review of the chemotherapy literature carried out in the early 2000s concluded that combination therapy was likely to be more effective than single agent therapy [9]and shortly thereafter Vogelzang’s randomized comparison between cisplatin and cisplatin/pemetrexed confirmed cisplatin/pemetrexed as the new therapy standard. Thirteen years later this standard has been augmented by a large comparative French intergroup study revealing that the addition of bevacizumab to cisplatin/pemetrexed standard is associated with a 2.7 months advantage in median overall survival [10]. However, it is important to note that a not insignificant number of negative phase II and III studies with a range of inhibitors of growth factors including EGFR, VEGF and PDGF had preceded this positive result. Other targeted agents investigated in phase II and III studies including bortezomib, vorinostat, everolimus, and defactinib, the inhibitor of the NF2/mTOR/FAK pathway, have also failed to show notable activity in pre-treated MPM patients [11]. It has become clear that MPM is an immunogenic tumour type and the preliminary data showing responses after immune checkpoint (PD-L1) inhibition [12] seem to indicate that reversing the immunosuppression induced by advancing disease is likely to represent a major step forward. However, monotherapy with Tremelimumab, inhibitor of CTLA-4 and considered active in phase II studies, failed to produce a survival benefit over placebo in 2nd and 3rd line, underlining the importance of comparative studies [13]. Independent research groups have reported ‘spontaneous’ regression of MPM, revealed a relation between infiltrating lymphocytes and plasma cells and prognosis and presented promising early clinical results with mesothelin-targeting antibodies [11]. Most recently dendritic cell vaccination combined with pulsed (metronomic) cyclophosphamide to deplete regulatory T cells resulted in prolonged tumour control in a limited group of MPM patients [14]. It is not excluded that targeting multiple compartments involved in immune surveillance will lead to increased efficacy. Early signs of efficacy of experimental treatment with tumour suppressive microRNAs packaged in micelles [15, 16] and the interaction between the microRNA 15/16 family and PD-L1 expression point to the complexity of immune checkpoint regulation and underlines the need for additional translational studies to unravel the resilient drug resistance mechanisms operable in MPM. 1. Marinaccio, A., et al., Malignant mesothelioma due to non-occupational asbestos exposure from the Italian national surveillance system (RenMa): epidemiology and public health issues. Occup Environ Med, 2015. 72(9): p. 648-55. 2. Takahashi, K., P.J. Landrigan, and R. Collegium, The Global Health Dimensions of Asbestos and Asbestos-Related Diseases. Ann Glob Health, 2016. 82(1): p. 209-13. 3. Bueno, R., et al., Comprehensive genomic analysis of malignant pleural mesothelioma identifies recurrent mutations, gene fusions and splicing alterations. Nat Genet, 2016. 48(4): p. 407-16. 4. de Reynies, A., et al., Molecular classification of malignant Pleural mesothelioma: identification of a poor prognosis subgroup linked to the epithelial-to-mesenchymal transition. Clin Cancer Res, 2014. 20(5): p. 1323-34.
PC01.02 INVASIVE STAGING AND RESTAGING
Christophe Dooms
University Hospitals KU Leuven, Leuven/Belgium

The aim of mediastinal staging is to exclude with the highest certainty and the lowest morbidity patients with mediastinal nodal disease. The concepts of decision analysis and Bayes’ theorem form the basis for a mediastinal staging strategy. The goal of the clinical staging strategy is to lower the post-test probability sufficiently so that it falls below a testing threshold, which is then considered the point of cut-off for mediastinal staging. There is no evidence to suggest that sampling of all visible nodes is feasible but some primary choices have to be made. At least mediastinal nodal ultrasonography (EBUS) has been introduced leading to video-assisted mediastinoscopy (VAM) clearly improving visualization and teaching. In addition, VAM allows bimanual dissection with possibilities to perform nodal dissection and removal rather than sampling or biopsy. The ESTS working group recommends performing VAM. Endoscopic ultrasonography (EUS) end bronchial ultrasound (EBUS). In the last decade, the predominant role of cervical mediastinoscopy. A conventional cervical mediastinoscopy through a pretracheal suprasternal incision was introduced in 1959 and for decades considered the gold standard for invasive mediastinal nodal staging. Recently, a large (N=721 patients; prevalence of mediastinal nodal disease 4.7%) retrospective single center study reported on safety and efficacy of cervical mediastinoscopy performed by general thoracic surgeons. There was no mortality, a low perioperative complication rate at 1.3 %, and an unexpected hospital (re)admission rate of 0.66 %. The sensitivity, negative predictive value and post-test probability were 0.90 (95% CI 0.87-0.92), 0.92 (95% CI 0.90-0.94), and 0.09 (95% CI 0.07-0.11), respectively. It is performed under general anesthesia and allows a full mapping of the ipsilateral and contralateral superior mediastinal lymph nodes. Since 1995, the use of video techniques has been introduced leading to video-assisted mediastinoscopy (VAM) clearly improving visualization and teaching. In addition, VAM allows bimanual dissection with possibilities to perform nodal dissection and removal rather than sampling or biopsy. The ESTS working group recommends performing VAM. Endoscopic ultrasonography (EUS) end bronchial ultrasound (EBUS). In the last decade, the predominant role of cervical mediastinoscopy has been challenged by EUS and EBUS using a convex probe. While cervical mediastinoscopy is required in scenarios of mediastinal nodal staging or in situations of feasi able but some primary choices have to be made. At least mediastinal nodal stations 4R, 4L and 7 should be sought. To avoid contamination, the order of sampling should begin at the level of N3 stations followed by N2 stations before N1. There is no evidence to suggest that sampling of all visible nodes in each nodal station is superior to cervical mediastinal nodal sampling, especially the largest measuring ≥5 mm or PET-positive node in each station. It must be stressed that EBUS cannot access the prevascular nodes (stations 3a), the subaortic and para-aortic nodes (stations 5 and 6) as well as the paraaortic and pulmonary ligament nodes (stations 8 and 9). Some of these nodes (stations 8 and 9) can however be reached from the esophagus. Therefore the use of the EBUS scope is extended to an esophageal exploration with EUS-B. Therefore the use of the ESTS scope is extended to an esophageal exploration with EUS-B and 9) can however be reached from the esophagus. Therefore the use of the EBUS scope is extended to an esophageal exploration with EUS-B. Therefore the use of the ESTS scope is extended to an esophageal exploration with EUS-B and 9) can however be reached from the esophagus. Therefore the use of the EBUS scope is extended to an esophageal exploration with EUS-B. Therefore the use of the ESTS scope is extended to an esophageal exploration with EUS-B and 9) can however be reached from the esophagus. Therefore the use of the EBUS scope is extended to an esophageal exploration with EUS-B. Therefore the use of the ESTS scope is extended to an esophageal exploration with EUS-B and 9) can however be reached from the esophagus.
will develop resistance. While predicting the future is usually only a fool’s errand, the past is prologue. So, what is the future of chemotherapy in NSCLC? Better drug delivery systems; developing combination therapy with DNA repair inhibitors, cell cycle checkpoint modulators, and immunotherapeutics; and improved biomarkers for efficacy and toxicity are each on the horizon. Improved targeting of the cancer cell, increased cancer cell drug concentrations, and reduction of normal cell toxicity can be accomplished through nano-carriers. Nano-carriers can deliver chemotherapy directly to cancer cells and avoid agents that are responsible for the toxic effects of chemotherapy. Another strategy to enhance drug delivery to tumors is through antibody-drug conjugates (ADCs). These agents link an antibody to a protein overexpressed on the surface of a cancer cell to a potent cytotoxic such as a microtubule inhibitor or an alkylating agent. The cytotoxic is released only in the cancer cell after the ADC complex is internalized. Examples include TDM-1 and Brentuximab. Over 30 ADCs are under clinical investigation, including several against lung cancer including Rova-T and Saelitzumab.

Another promising strategy for the future treatment of lung cancer involves combining chemotherapy with drugs that interfere with DNA repair, silence DNA repair genes, or inhibit cell cycle arrest. Examples of this approach include PARP inhibitors, DNA methylation agents, and checkpoint modulators. Combination trials of chemotherapy and immunotherapy are also underway. In this regard, ADC technology may prove a more effective strategy when combining cytotoxic drugs with immunotherapy. By improving chemotherapy drug delivery to cancer cells and reducing off-target toxicities, nanotechnology has the potential to most effectively combine chemotherapy with immunotherapy. In the last decade, the vast majority of the available immunotherapies for lung cancer, the majority of patients are empirically treated with chemotherapy, regardless of the molecular characteristics of the tumor and the pharmacogenomics of the patient. Refrains in these areas are expected in the upcoming years. In conclusion, for better or worse, in the year 2030 chemotherapy will remain standard of care for the majority of patients with stage I-IV NSCLC. But, the year 2040 or 2050 may be a different story.

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MERCK press release, July 2016

Hellman MD, Gettinger SN, Goldman JW, et al. CheckMate 012: Safety and efficacy of first-line (1L) nivolumab (nivio; N) and ipilimumab (ipi; I) in advanced (adv) NSCLC. J Clin Oncol 34, 2016 (suppl; abstr 3001).

Keywords: Immunotherapy, Targeted therapy, lung cancer
In the diagnosis of lung cancer the primary diagnostic approach is microscopic evaluation of tissue biopsy. However, in many cases the only material for microscopic evaluation is cytological one. There are numerous types of cytological material in evaluation of lung tumors including sputum, bronchial brush, bronchial washing, transthoracic and transbronchial fine needle aspirates. Historically sputum was the most common diagnostic material but at present the most common types of cytological specimen are bronchial brush, and transthoracic or transbronchial FNAB. Nowadays worked out and recognized cytological criteria allows not only to diagnose carcinoma but in majority of cases to specify the histologic type of a tumor. This approach to cytological evaluation of lung carcinoma was incorporated to the latest WHO classification of lung tumors (ref). The key that cytodiagnostic criteria and terminology were included into WHO classification was that in about 30% cases of lung tumors the cytological specimen is the only material for the differential diagnosis of early stages. Similar to evaluation of small tissue biopsies in histopathology, in doubtful cases, immunocytochemistry may be implemented to determine histologic type of tumor. Most useful in evaluation of cytological specimen are IHC antibodies with nuclear presentation. (e.g. p53 for squamous cell carcinoma and TTF1 for adenocarcinoma). Cytological material may be utilized in evaluation and in differential diagnosis between primary and metastatic lung tumor. The panel of the antibodies (e.g. CDX2, PSA, Melan A) may be used to indicate location of primary tumors mainly adenocarcinomas. Since cytological smears are of limited diagnostic value for immunocytochemistry, the so-called cell block technique is recommended. This technique allows to use larger panel of antibodies for immunohistochemical evaluation. Cytology become very useful for clinical staging of lung carcinoma routinely utilizing EBUS and EUS technique for obtaining material from parahilar and mediastinal lymph nodes. Cytological criteria are similar to that used for specimens obtained by transthoracic FNAB. In our center practice cooperation with adequately trained thoracic surgeons provides adequate material for microscopic evaluation from EBUS and EUS obtained specimens in 94% cases. Currently one of the important task for pathologist in evaluating material from lung carcinoma is adequate selection of the material for molecular test. In case of lung carcinoma or to be specific lung adenocarcinoma a material is selected for evaluation of EGFR and K-RAS mutation. In our experience cytological material particularly fine needle aspirates - fulfill such demands. Percentages of tumors cells in the sample is often even higher than in tissue sections especially in fine needles of the peripheral location. Cytological material may be useful in evaluation of EGFR and K-RAS mutation as well as in determination of presence of translocations of ALK and ROS1 using FISH technique. Evaluation of ALK and ROS1 translocation remained in the hands of cytopathologists since the crucial point is the location of translocation in nuclei of tumors cells. Latest challenge for pathologists evaluating lung carcinoma specimens is to determine predictive criteria for immunotherapy in those tumors. At the moment it seems that cytological material may be not satisfactory for adequate evaluation of immunocytochemical expression of PD1 and PD-L1. In summary cytological material from lung carcinoma is useful in establishing the microscopic diagnosis of malignancy, to determine histologic type and to be used for molecular tests. It also allows to differentiated between primary and metastatic lung malignancies as well as determined primary location of metastatic lung carcinoma. Cytological specimens obtained by EBUS and EBUS techniques are very useful in clinical staging of lung carcinoma. Reference Travis WD, Brambilla E, Burke AP, Marx A, Nicholson AG eds. WHO Classification of Tumours of the Lung, Pleura, Thymus and Heart. 4th ed. Lyon, France: IARC Press; 2015

Keywords: cytology, lung carcinoma, molecular testing

SESSION IA05: THE PRACTICAL USE OF THE TNM CLASSIFICATIONS FOR THORACIC CARCINOMS

TUESDAY, DECEMBER 6, 2016 - 11:00-12:30

IA05.01 LUNG CARCINOMA CASES

Gustavo Lyons

The definition of staging in Lung Cancer is the determination of the anatomic extent of three tumor components: the primary tumor (T), the lymph nodes (N), and the metastases (M). Their accurate evaluation allows grouping patients in stages that is one, and perhaps the single most important, of several prognostic factors that guide the appropriate treatment option(s) to offer the patient. The clinical classification cTMN (Pre-treatment clinical classification), is based on evidence acquired before treatment. The pathological classification pTMN (Post-surgical histopathological classification), is based on the evidence acquired before treatment, supplemented or modified by the additional evidence acquired from surgery and from pathological examination of the involved sites. A minimum number of tests is not required to define the extent of the disease, but it’s very clear that as more exhaustive the explorations more accurate and precise the staging will be. This may be strongly affected by the availability of physical and human resources, multidisciplinary work and adherence to clinical practice guidelines. After the changes proposed by the new IASLC/ATS/ERS Lung adenocarcinoma classification and the IASLC proposals for revision of the T, N and M descriptors and stage groupings in the forthcoming (Eighth) edition of the TNM Classification for Lung Cancer, we must incorporate this new reclassification into our clinical practice. (1, 2) The changes that The IASLC Staging Committee recommends for the T, N and M descriptors and the resulting new stage grouping and their survival are summarized in table 1 and figure 1. The main changes in T Components are the relevance of the size of the tumor for each cm, grouping of the involvement of the main bronchus or partial and total atelectasis on one side. (3, 4) For the new stage grouping, the new size cut points of T1N0-M0 tumors has been assigned to stage IAI, IA2, and IA3. The new stage IIIC (T3 and T4-N3-M0) reflects their worse outcome. Finally, stage IV disease has been divided into IVA (M1a, M1b) and IVB (M1c). The new IVA stage grouping should be used in trials analyzing patients with other neoplasms or concomitant cardiovascular disease. (2) For the need of each described types of adenocarcinoma of the lung, the IASLC recommends incorporating the coding of AIS as Tis (AIS) and of MIA as T1mi into the traditional TNM classification. For solid-tumors, the size of the invasive component should be used to assign a T category, but the whole tumor size should also be recorded. However, the measurements will be influenced by the number of observer-dependent and technical factors. It is important to perform the measurements for clinical staging on contiguous thin CT sections reconstructed with a high-resolution algorithm with multplanar reconstruction. (6) For pathologic staging, attention should be given to the assessment of invasive and epithelial lesions. It can be helpful to correlate microscopic findings with measurements made on gross examination, particularly in inflated specimens or with CT findings. Patients who present with more than one pulmonary site of lung cancer may represent different patterns of disease as synchronous primary lung cancer, separate solid tumor nodule(s) (intrapulmonary metastases), multifocal lung cancer presenting as multiple nodules with ground glass/lepidic features, and diffuse pneumonic-type adenocarcinoma. It is proposed that the T category of patients presenting ground glass/lepidic (GG/L) tumors be classified using the following scheme: the highest T category lesion in parenchyma (not with GG/L tumors or simply m for multiple m/PM). A single N and M category is assigned for all GG/L tumors combined. (7) Both clinical information (the presence of additional lesions identified by imaging) and the pathologic information (from resected lesions) should be used to determine the TNM classification. Lesions smaller than 5 mm or AAH are not counted. The pneumonic type of adenocarcinoma should be classified according to the size of the area of lung involved, or as T4 or M1a in the case of involvement of more than one lobe, either (isiliparal or contralateral). A single N and M category is assigned. In patients with separate tumor nodules (intrapulmonary metastases), minimally proposed that these be code using TNM classification of same-lobe nodules as T3, same side (different lobe) nodules as T4, and other-side nodules as M1a be carried forward. (8) It is easier to establish that two pulmonary foci of cancer are separate primary tumors than that they are metastatic from another. Few features are sufficient to establish that two tumors are truly separate. These features include the presence of a transbronchial nodule, the location of the nodules, the presence or absence of nodal involvement. The fact that generally only biopsy specimens are available at the time of clinical decision making further adds to the uncertainty and difficulty of the assessment. A constellation of factors is better than any single factor; it is best to make a determination of separate primary versus metastatic lesions through a collective judgment of a multidisciplinary tumor board after taking into account all of the available information. (9) Synchronous primary cancers are classified with a T, N, and M category for each tumor; separate tumor nodules result in a T3, T4, or M1a category depending on the separate nodule’s location relative to the primary tumor.
(10) Despite these proposals of staging, there will always be areas of difficulty and tumors that are challenging to classify. The prognostic value of clinical and pathological TNM staging in patients with SCLC was also confirmed, and the continued usage is recommended in relation to proposed changes to T, N, and M descriptors for NSCLC in the eighth edition. (11) Table 1

<table>
<thead>
<tr>
<th>T categories</th>
<th>Description in 7th edition</th>
<th>Proposed TTM</th>
<th>N categories</th>
<th>Overall stage</th>
<th>N0</th>
<th>N1</th>
<th>N2</th>
<th>N3</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1a</td>
<td>1 cm</td>
<td>Ia1 (A)</td>
<td>IB (B)</td>
<td>IA</td>
<td>A</td>
<td>B</td>
<td>B</td>
<td>B</td>
</tr>
<tr>
<td>T1b</td>
<td>≥1 - &lt;2 cm</td>
<td>Ia2 (A)</td>
<td>IB (B)</td>
<td>IA</td>
<td>A</td>
<td>B</td>
<td>B</td>
<td>B</td>
</tr>
<tr>
<td>T1c</td>
<td>≥2 - &lt;3 cm</td>
<td>Ia3 (A)</td>
<td>IB (B)</td>
<td>IA</td>
<td>A</td>
<td>B</td>
<td>B</td>
<td>B</td>
</tr>
<tr>
<td>T2</td>
<td>≥3 - &lt;4 cm</td>
<td>IB (B)</td>
<td>IB (B)</td>
<td>IA</td>
<td>A</td>
<td>B</td>
<td>B</td>
<td>B</td>
</tr>
<tr>
<td>T3a</td>
<td>≥3 - &lt;4 cm</td>
<td>IB (B)</td>
<td>IB (B)</td>
<td>IA</td>
<td>A</td>
<td>B</td>
<td>B</td>
<td>B</td>
</tr>
<tr>
<td>T3b</td>
<td>≥4 - &lt;5 cm</td>
<td>IB (B)</td>
<td>IB (B)</td>
<td>IA</td>
<td>A</td>
<td>B</td>
<td>B</td>
<td>B</td>
</tr>
<tr>
<td>T4a</td>
<td>≥5 cm</td>
<td>IB (B)</td>
<td>IB (B)</td>
<td>IA</td>
<td>A</td>
<td>B</td>
<td>B</td>
<td>B</td>
</tr>
<tr>
<td>T4b</td>
<td>Multiple lesions</td>
<td>IA (B)</td>
<td>IB (B)</td>
<td>IA</td>
<td>A</td>
<td>B</td>
<td>B</td>
<td>B</td>
</tr>
<tr>
<td>T4c</td>
<td>Multiple lesions</td>
<td>IA (B)</td>
<td>IB (B)</td>
<td>IA</td>
<td>A</td>
<td>B</td>
<td>B</td>
<td>B</td>
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</tbody>
</table>

Table 1: Descriptors and N Categories for NSCLC in the Eighth Edition. (11)

Where there is a change, the resultant stage groupings proposed for the eighth edition are in bold, and the stage in the seventh edition is given in parenthesis. Figure 1 Overall survival by clinical and pathological stage according to the proposed eighth edition groupings using the entire database available for the eighth edition.

References:


Keywords: Staging, TNM, Mesothelioma
Despite substantial reductions in smoking prevalence, lung cancer is the leading cause of cancer-related mortality for both genders in the United States. In 2016, lung cancer is expected to be responsible for 158,080 deaths. Tobacco smoking is still the number one risk factor for lung cancer and has been linked to 90% of all lung cancer cases. Currently, only 15% of all lung cancer cases are diagnosed at an early stage. Historically, these poor rates were due to the lack of effective routine screening. This changed dramatically in November 2011 when the National Lung Cancer Screening Trial (NLST), released their results that showed low-dose computed tomography (LDCT) could reduce lung cancer mortality by 20%. LDCT is now widely recommended for current and former smokers. Identification of all barriers and facilitators is essential for the successful promotion of lung cancer screening.

Denormalization of smoking has been one of the most successful tobacco control measures and has resulted in a sharp decrease in the prevalence of smoking. It is now concentrated in the most vulnerable populations (e.g. lower income groups and the mentally ill) who have the least ability and/or willingness to quit. In addition, denormalization has the effect of sanctioning smoking related stigma. A majority (95%) of lung patients expect lung cancer, with 48% of lung cancer patients specifically reporting feeling stigmatized by their medical providers. Perceived lung cancer stigma is a risk factor for poor psychosocial and medical outcomes in the context of lung cancer diagnosis and treatment. People often associate lung cancer with previous smoking behavior, regardless of whether the person with lung cancer was a smoker or not. There is growing body of evidence that patients, caregivers, healthcare providers, and family members experience stigma as a result of the lung cancer diagnosis.

In our previous work we found that there were four beliefs associated with whether older (≥55) current and former smokers would agree to lung cancer screening (LDCT): Perceives accuracy of the LDCT as an important factor in the decision to have a LDCT scan, Believes that early detection of LC will result in a good prognosis, Believes that they are at high risk for lung cancer; and is not afraid of CT scans. This study showed that older smokers are aware of the risks of smoking, are interested in smoking cessation, and most are interested in and positive about LDCT. There are no studies that have examined the impact of perceived lung cancer stigma on the decision to have an LDCT. To address this gap, we conducted a secondary analysis in which lung cancer stigma was measured by five true or false items: doctors treat smokers badly; doctors have a bias against smokers; cigarette smokers keep their smoking a secret from important people in their lives; cigarette smokers avoid talking about smoking with their doctor; cigarette smokers feel guilty about their smoking; and friends and family are upset that I smoke. Four variables demonstrated a significant association with LDCT agreement: People treat smokers badly; Doctors have a bias against smokers; Smokers feel guilt about smoking; and Friends and family do not approve of my smoking. Only two of the independent variables made a unique statistically significant contribution to the model. A test of the model against a constant only model was statistically significant, indicating that the predictors as a set, reliably distinguished between those who would agree to an LDCT and those who would not agree (chi square = 8.5 p. = 0.003). The odds ratios for the remaining predictor, Doctors have a bias against smokers, was OR 1.7, 95% CI 1.47- 4.90); Believes that they are at high risk for lung cancer was OR 2.1, 95% CI 1.8 – 3.12). The decision to agree to an LDCT is negatively associated with two indicators of perceived stigma, “people treat smokers badly” and “doctors have a bias against smokers.” These findings support that denormalizing smoking stigma is a barrier to lung cancer screening and thus far participation in trials has been skewed towards former smokers and better educated smokers. With the current demographic profile of smokers, the effectiveness of a lung cancer screening program depends in part on whether there are inequalities in participation which has the potential to exacerbate disparities in lung cancer survival. Given the impact of lung cancer stigma on satisfaction with care and patient outcomes it is imperative that further research explore the association of perceived lung cancer stigma and the decision to have LDCT.
SESSION NU02: PREPARING PATIENTS FOR TREATMENT
MONDAY, DECEMBER 5, 2016 - 16:00-17:30

NU02.01 PREPARING PATIENTS FOR TREATMENT. PROVIDING PSYCHOSOCIAL SUPPORT FOR LUNG CANCER PATIENTS
PREPARING TO ENTER TREATMENT
Andrea Cirila Škufca Smrdel

Keywords: lung cancer, Indigenous

Abstracts
Journal of Thoracic Oncology  •  Volume 12 Issue S1 January 2017

Background: Lung cancer and its treatment have a major physical impact, as well as emotional, social, psychological, spiritual, functional and practical challenges and consequences, both for the patient and his relatives. While coping with the disease they become aware of vulnerability and mortality, they are facing hope and the mortality of their loved ones which patients which are harbouring could be an important factor at coping with the lung cancer. Both smokers (or former smokers) and non-smokers are being stigmatised, and lung cancer is connected with stereotype representation of incurable disease(2). Life is never the same as before the diagnosis. In the comprehensive approach to the lung cancer, team work is of the utmost importance. Beside the standard oncological treatment, for the patient there is a benefit of an early palliative care. This benefit besides better quality of life (due to better quality of life, less depression and less aggressive treatment) confers also an increase of survival(3). Here, the nurse is an important member of comprehensive cancer team, and is the one spending the greatest amount of time at bedside. Methods: We reviewed the literature and the current clinical practice. Results: In operationalising psychosocial care in oncology many authors are advocating so titled approach(4,5). Providing psycho-social support to lung cancer patients is the task of all medical workers included in the multidisciplinary care. At all cancer patients have the basic psycho-social needs, such as informational needs, basic emotional support, adequate communication, screening of needs on-going basis and the symptom management. Patients experiencing more profound distress or have more unmet needs, should be directed to the specialist team. Here mental health or professional needs or professional needs. At the psycho-social care of the lung cancer patients entering the treatment, there should be an emphasis on the adequate patient information concerning the disease, planned treatment, side effects and their management, the possibilities of patient's contribution to the treatment, and also the patient's existential issues should be addressed. It is important for the patient to get as much information as he deems necessary, being careful about the pace the information is given. Despite the amount of information offered in media in the recent time – many of them unfortunately also untested – many patients in their search for information forget getting information from health professional with communication with health provider, in relation with whom they are experiencing confidence, safety, care and professionalism(1). It is important to present the information, at the same time accurate and still preserving the hope even in the face of the odious situation, thus giving the patient and his relatives emotional support and strengthening their coping strategies. Therefore, medical professionals should develop good communication skills; these are proven to be associated with less unmet needs(6).The patient and also with the increase of informed decisions regarding treatment(7). In patients with poorer communication skills, adequate supportiveness can help with the patient's treatment and will help the medical professionals but also with the relatives. The cognitive behavioural therapy strategies can take a pivotal role. Cognitive interventions are focused on the way of thinking about a situation and through it influences the behavioural and emotional response; like the structure of their environment, the development of positive alternative to negative thought, or distraction, changing the patient focus. Behavioural interventions, such as relaxation techniques, can help controlling physiological responses in stressful situations. An important issue in the support of patient's psycho-social needs is including in consideration emotional and social re-constructive factors, like patient's relatives, friends and peers, medical workers represent an integral part of it. In the patient's preparation for treatment, it is important to recognize those experiencing more profound distress or having more unmet needs, thus needing more help. Research has shown that cancer patients are experiencing more physical problems - the most common are pain, dyspnoea, fatigue, cough(8) – and also have more unmet needs than other patients. In excess of 80% of lung cancer patients are experiencing some degree of psychological distress. This is more than other cancer type patients are experiencing. Depression estimates are ranging between 11 and 44% and the fear of recurrence is ranging between 61 and 87(9). The severity of distress is varying through the process of treatment and rehabilitation; the time of diagnosis is a period during which more patients are entering psycho-social treatment than later during treatment(10). With the aim of early recognition of patients with more profound distress, screening procedures are being implemented. Beside different questionnaires, International Psychosocial Oncology Society is striving to implement the distress thermometer with 10 grades(10). The psycho-social interventions, performed by mental health professionals are proven to increase wellbeing, improve adjustment and coping, and reduce distress in people with cancer. In the field of psycho-oncology, the most commonly used methods are cognitive behavioural therapy, learning of relaxation skills, psycho education, and also partnership and family therapy(11). Providing psycho-social treatment for patients with more profound distress is connected with multiple challenges. Beside patient recognition and implementation of screening programmes, the next challenge is patient's compliance, as psychological treatment can for a patient still be stigmatised. Despite limited evidence of its efficacy patients prefer emotional and social help from the nurse than from allied professionals, because their medical expertise is seen as an advantage(12). In many healthcare systems the...

NUO2.02 PREOPERATIVE THORACIC SURGERY PATIENT EDUCATION PROGRAM DEVELOPMENT

Katherine Kuhns
Thoracic Surgery, Nursing, Penn Presbyterian Medical Center, Philadelphia/PA/ United States of America

Purpose: To develop a cost-effective preoperative patient teaching program that includes a patient teaching video along with written material that improves patient satisfaction, decreases patient readmission rates associated with post-operative complications, and optimizes overall outcomes of thoracic surgery patients. Overview: Patients undergoing surgery usually have little knowledge of what to expect during the preoperative, postoperative, and recovery period following thoracic surgery. Conclusion: Providing patients with multi-format education materials and the ability to review them on their own time has proven successful at achieving the stated goals. Moving forward we intend to build upon this resource to improve the patient education program at our institution. Additionally, we hope to conduct a formal research project in conjunction with other institutions as such to better understand how to develop thoracic patient education and to help identify which programs work best in promoting patient education and changing behaviors in the thoracic surgery population.

Keywords: Patient Education Thoracic Surgery

NUO2.03 ETHICAL DECISION MAKING

Sabine Ruppert
Department of Medicine I and Department of Medicine III, Division of Nephrology and Dialysis, Vienna General Hospital, Vienna/Austria

Ethical decision making is very important in the context of treatment of cancer patients. These decisions can lead to withdrawal or withholding of life sustaining therapy, or change the goal of the therapy from curative to palliative. “Do-not-reanimate” or “allow-natural-death” orders are also part of ethical decision making. Sometimes pain treatment is adapted or palliative sedation is started. It is necessary to make these decisions to ensure dignity at the end-of-life, which is a human right. Ethical decision making is usually done by the state-of-the-art in the context of Palliative Care. It is in close contact with the patient, the next of kin and other health-care-professionals involved in the treatment. The decision making process is structured, documented and can be replicated for everyone. Most of the time, these decisions are made by physicians only, without a dialogue, especially in Austria in hospitals in nursing homes. Sometimes they are not shared with the patient’s relatives. Physicians rarely ask other health-care-professionals for their opinion. End-of-life-decision-making seldom occurs as a structured well documented process. But the fact, that by law physicians have to take the final decision, does not prevent them from listening to and involving the perspective of the different persons concerned. If the discussion stops with the question “Who is allowed to decide?” then decisions would only be
made because of having legal authority and not because of ethical reasons. (Vanlaere & Gastmans, 2008, Arndt, 2007) From an ethical perspective these decisions are often decisions between the autonomy of patients and the care of health care professionals. It is crucial to preserve the dignity of the suffering human being. It is a challenge to make reasonable ethical decisions in a context characterized by strong pressure for efficient and flexible organisational structures on the one side and complex values on the other side. (Gastmans & Vanlaere, 2005). It is not always clear what is right and what is wrong, or what is good and what isn’t. Sometimes health care professionals, especially physicians, try to avoid these decisions by not deciding anything, but avoidance is also a decision. Ethical decision making is much more difficult, if the suffering person cannot express his wishes anymore. Then, physicians and other health care professionals, who are included in the decision-making process, have to find out the person’s wishes. It is very important that ethical decision making is based on indication for treatment, futility and the wish of patient. (Bundeskanzleramt, 2015) Ethical decision making should include all persons involved – physician, patient, relatives, nurses and also, if appropriate pastor or other religious leader, social workers and other health care professionals. The involvement of patients and – if they wish – their next of kin is necessary. Austrian medical guidelines (Valentin et al. 2004) recommended that nurses and other members of the multidisciplinary team had to be involved in such decisions. The decision making process should be structured, documented and - dependent on the context of the decision process, – visible. Several tools exist for ethical decision making and help to guide and structure the dialogues. Individual ethical case conferences could be part of clinical ethical counseling, which also includes ethical education and providing guidelines. (Zentrale Ethikkommission, 2006) Examples of such decision-making-models are the model of Gastmans and Vanlaere (Vanlaere & Gastmans, 2008) based on the personalism and care-ethic, the Nijmegen-model of Steinkamp and Gordijn (Steinkamp, 2012) and the model of Arndt (2007). Decision-making-models are not simply checklists. Health care professionals have to use them with empathy in the context of their own experience and values. (Körtner, 2012) General guidelines could deviate from frequently arising problems, but there always would be individual cases, which represent marginal cases because they burst all limits (Körtner, 2012). By using decision-making-models health care professionals have to be alert, not to use those strictly according to the written instructions. The sensitivity for the individual and his specific situation has to be preserved. A discussion or counselling, where all persons concerned make a choice together according to their values and principles, is the best guarantee for a well-grounded ethical decision and gives more sense of security for a good result. Nevertheless, there is no guarantee for a right or good decision. (Körtner, 2012) Because of the emotional burden of end-of-life-decisions, these models are also helpful to include all important aspects. The participants of these dialogues have to respect the values of the others and to see the situation from their point of view. Using decision-making-models guarantees to involve all relevant individuals. Furthermore, the decision making-models are better understandable and visible. Finally, it is important to mention that ethical decision making can’t be reduced to decision-making-models. Ethical thinking is a result of dynamic mutual reactions between emotions, intuition, standardization and rational reasoning. (Van der Arend & Gastmans, 2009) The role of nurses in this decision making process and also in the realization of these decisions is rarely recognized. But nurses play an important role in ethical decision making - as national leader, social workers and other health care professionals. They communicate to this study and the plan is to proceed to full trial. This paper presents 2012, Horton 1996). Potential solutions for this include restrictive trial regulation, patients declining randomisation, and difficulties in recruitment practice such as presenting trial arm options neutrally (Treasure & Morton 2012). The Mesoethioma and Radical Surgery 2 (MARS 2) Trial, a UK based study, will evaluate whether EPD can improve the length and /or quality of life in patients with surgically treatable disease and its cost-effectiveness. It will randomise participants to chemotherapy or chemotherapy plus surgery. The feasibility stage has demonstrated the ability to recruit and randomise to this study and the plan is to proceed to full trial. This paper presents findings from a nested patient experience sub-study within MARS 2 that investigated patient experience of the study interventions. It more specifically identifies the support and information needs for people regarding i) the interventions (surgery and chemotherapy) and ii) trial recruitment, consent and participation. This paper focuses on the findings related to support needs of the trial interventions. A summary of results will be provided along with reflections on the implications for future practice. Methods: An in-depth longitudinal qualitative study with interviews of 16 participants randomised to chemotherapy (n=8) and chemotherapy + surgery (n=8). Interviews were conducted after randomisation (but before surgery in the surgical cohort). Surgical patients had an additional interview post surgery. Framework analysis methods were used (Ritchie and Lewis, 2014). Follow-up interviews were at 6 and 12 months post-randomisation. This paper presents findings up to and including the 6 months follow-up. Results: Participants reported being well informed about their illness, but had struggled to absorb and understand the extent of information delivered at diagnosis. This was influenced by the range of significant subjects that were covered in a number

SESSION NU03: SUPPORTING PATIENTS RECEIVING TREATMENT
Tuesday, December 6, 2016 - 11:00-12:30

NU03.01 SUPPORTING PATIENTS UNDERGOING RADICAL TREATMENTS EPD – MARS STUDY
Angela Tod
School of Nursing and Midwifery, The University of Sheffield, Sheffield/United Kingdom

Abstracts

TUESDAY, DECEMBER 6, 2016 - 11:00-12:30

S103

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Background: Malignant pleural mesothelioma (MPM) is an aggressive cancer of the lining of the chest wall and lung, its aetiology lies in asbestos exposure. With over 2,500 people diagnosed each year, the UK has the highest incidence of mesothelioma in the world. Chemotherapy is an established treatment for MPM but response rates are variable, evidence is lacking in new drug therapies and mortality remains high (in the UK half of patients die within 8.5 months of diagnosis) (Maggioni 2016, HSCIC 2015). Surgery is therefore an important option. Very little robust, randomised controlled trial evidence (RCT) exists regarding surgical interventions for mesothelioma and many studies are observational (Cao et al 2016). This has prompted global variations in surgical approaches (Mclean 2013). Extended Pleurectomy Decortication (EPD) is a surgery for patients considered to have resectable MPM. EPD involves the removal of the lining of the chest wall, lining of the lung, with the sac of the heart and/or diaphragm (as required to achieve complete tumour removal) but leaving the lung in-situ. However, evidence on survival or symptom improvement benefits of this surgery is limited (Cao et al, 2014, Teh et al 2011). Challenges in surgical research are the lack of clinical trials and few patients choosing to enter RCTs for surgery (Treasure & Morton, 2012) and the understand the extent of information delivered at diagnosis. This was influenced by the range of significant subjects that were covered in a number


Keywords: end-of-life-decisions, decision making process, role of nurses, palliative care
of consultations with different healthcare staff providing different specialist services. The topics discussed included diagnostic information about mesothelioma, treatment options and consequences, trials processes and logistics, legal and financial information regarding classification of MPM as an industrial disease. Despite feeling well informed about their treatment some participants reported not being prepared for the full extent of the problems they experienced. Both chemotherapy and surgery were challenging treatments although they were associated with different physical effects. Adverse consequences of treatment were described including neutropenic sepsis and dehydration post chemotherapy, and bleeding, prolonged pneumothorax and infection post-surgery. For most participants pain and breathlessness were experienced post-surgery while nausea, anorexia, taste changes and constipation were associated with chemotherapy. Fatigue that impacted on daily living was experienced by both groups. Interventions to manage the consequences of treatment were recounted; some had been recommended by healthcare staff while others had been developed by patients from their own initiative. Participants reported struggling to cope with the effect of treatment whilst trying to deal with the broader context of coming to terms with their illness. Uncertainty was expressed in relation to treatment plans (exacerbated by the logistics surrounding participation in a clinical trial), severity and duration of side effects, rehabilitation and recovery and treatment outcomes. Participants employed a number of strategies to help with coping. These included ‘playing things down’, ‘weighing the balance’, ‘managing expectations’, ‘taking control’, ‘managing up’ and ‘trust in the doctor and/or treatment’. Many of these strategies facilitated staying positive, maintaining hope and finding comfort which was important to participants. Family members played a key role in coping. A diverse range of healthcare professionals provided information and advice and practical interventions across the care pathway from community, surgical, respiratory and oncology services. Discussion: Patient’s perspectives on the experience of receiving radical surgery and/or chemotherapy for mesothelioma were identified by the study. This provided valuable insights into their impact on patient’s feelings about their illness and treatment and how they coped with the challenges they were presented with. Multiple sources of uncertainty were expressed by participants. The contribution of healthcare staff to supporting coping and providing information and advice was appraised positively by participants. However, we identified that fragmentation could occur due to the diverse care is therefore vital in this patient group. Patient Reported Outcome Measures (PROMs) can be used to identify the supportive care needs of people with lung cancer and the collection of PROMs data is reported to have a number of positive effects on patient outcomes. Enhancing the utility of PROMs within clinical practice is the use of health technologies that have the ability to collect PROM data remotely from patients in their own homes and send this information in ‘real-time’ immediately to relevant health/social care professionals for subsequent intervention. The Advanced Symptom Management System is one of the most evolved remote patient monitoring systems in cancer care. This presentation will initially focus on remote patient monitoring within the context of lung cancer before considering the practical implications for service improvement.

**Keywords:** Radical surgery, Mesothelioma, patient experience, Qualitative research

**NU03: SUPPORTING PATIENTS RECEIVING TREATMENT**

**TUESDAY, DECEMBER 6, 2016 - 11:00-12:30**

**NU03.03 EHEALTH AND REMOTE PATIENT MONITORING AND SUPPORTIVE CARE IN THORACIC ONCOLOGY**

Roma Maguire
School of Health Sciences, University of Surrey, Glasgow/United Kingdom

Lung cancer is the commonest cancer worldwide with 1.6 million people diagnosed each year. People with lung cancer experience a high level of supportive care needs and many of these needs are unmet. Systematic supportive care is therefore vital in this patient group. Patient Reported Outcome Measures (PROMs) can be used to identify the supportive care needs of people with lung cancer and the collection of PROMs data is reported to have a number of positive effects on patient outcomes. Enhancing the utility of PROMs within clinical practice is the use of health technologies that have the ability to collect PROM data remotely from patients in their own homes and send this information in ‘real-time’ immediately to relevant health/social care professionals for subsequent intervention. The Advanced Symptom Management System is one of the most evolved remote patient monitoring systems in cancer care. This presentation will initially focus on remote patient monitoring within the context of lung cancer before considering the implications for the future and the ultimate vision of connected health for all.

**Keywords:** Technology, connected health, lung cancer, supportive care

**NU03: SUPPORTING PATIENTS RECEIVING TREATMENT**

**TUESDAY, DECEMBER 6, 2016 - 11:00-12:30**

**NU03.04 SUPPORTIVE CARE IN PATIENTS RECEIVING SYSTEMIC THERAPY**

Tania Cufer
Medical Oncology Unit, University Clinic Goñik, Gašnik/Slovenia

Introduction Systemic therapy (ST) with chemotherapy (Cht), targeted agents or immunotherapy (IT) represents the mainstay therapy for patients with advanced lung cancer; while adjuvant systemic therapy is recommended in a majority of patients with operable and locally advanced disease. The goal of ST is to prolong life without compromising quality of life (QOL). Despite the ability of ST to prolong life or even cure patients, QOL and life span might be compromised due treat toxicity. In addition, uncontrolled adverse events (AEs) might lead to treatment interruption or discontinuation. Therefore, effective management of adverse events of anti-cancer drugs, the so-called “supportive care to systemic therapy” is extremely important for a treatment benefit, i.e. treatment effect in a routine practice. During the last decade several improvements in prevention, treatment and amelioration of ST AEs have been achieved. To implement them in everyday clinical practice a good understanding of adverse events, supportive care measures and professional skills of all team members are needed. Registered nurses, specialized in the oncology, the so-called “oncology nurses” are key providers of supportive care in everyday clinical practice. Supportive care for prevention and treatment of adverse events Chemotherapy-induced nausea and vomiting (CINV) has been a priority in the supportive care of cancer patients ever since the first use of Cht (1). The routine use of anti-emetic therapy resulted in much better control of CINV in lung cancer patients receiving highly emetogenic, platinum-based therapy. With proper use of available drugs complete control of vomiting could be achieved in up to 90% of these patients. However, despite the efficacy of new anti-emetics therapies a proper use of anti-emetics and other supportive measures are vital. Chemotherapy-induced neutropenia with febrile neutropenia (FN) as its ultimate and most serious complication are often observed in patients receiving Cht. The risk of FN can be predicted by assessing patient characteristics and myelotoxicity of the Cht regimen; and granulocyte-colony stimulating factors (G-CSF) can be used to prevent its occurrence. For most of the regimens for lung cancer do not classify to high, i.e. more than 20% risk of febrile neutropenia, the primary prophylaxis with G-CSF is often necessary due to high comorbidity index, poor PS or extensive disease often present in lung cancer patients. In case of FN, a risk base approach provided by MASC helps us to decide whether patients need higher dose of G-CSF or even high dose support with targeted therapy for lung cancer next to diarrhea. Even though, they are usually mild or moderate they have negative impact on patient’s QOL and might lead to dose modifications or even discontinuation. Prophylactic measures with regular use of moisturizing products, sunshine protection and careful skin hygiene are necessary. In case of severe but still localized changes topical corticosteroids/antibiotics are indicated while a severe and prolonged toxicity usually requires TKIs dose interruptions (6). Fatigue is a common symptom reported in up to 80% of LC patients. In most cases it is impossible to distinguish to what extend it is the adverse event of ST and to what of disease. It is increasingly reported in patients receiving targeted therapy or immunotherapy, and major improvements in recognition and treatment of fatigue have been achieved recently (7). Immunotherapy with checkpoint inhibitors (CPIs) represents a novel approach. By breaking of immune self-tolerance it might lead to the ability to collect PROM data remotely from patients in their own homes and send this information in ‘real-time’ immediately to relevant health/social care professionals for subsequent intervention. The Advanced Symptom Management System is one of the most evolved remote patient monitoring systems in cancer care. This presentation will initially focus on remote patient monitoring within the context of lung cancer before considering the implications for the future and the ultimate vision of connected health for all.

**Keywords:** Technology, connected health, lung cancer, supportive care
diagnosed with advanced non-small cell lung cancer (NSCLC) (either squamous or non-squamous) have previously had limited treatment options. With the emergence of new drugs, particularly in the immune-oncology setting, this is now changing. Recent clinical trial evidence demonstrates that combinations of drugs such as pembrolizumab and docetaxel, patients who received Nivolumab or Pembrolizumab had better overall survival and also significantly fewer Grade 3-4 adverse events (AEs). However the nursing experience of caring for lung cancer patients on an immunotherapy remains quite limited. Up to recent times immunotherapy drugs were limited to the clinical trial setting or early phase access schemes. Often patients on clinical trials are managed and monitored by researchers which can further limit the experience for Lung Cancer Clinical Nurse Specialists caring for patients on immunotherapy. The two main clinical trials for immunotherapy in the UK were CHECKMATE (Nivolumab) and KEYTRUDA (Pembrolizumab). The aim of this presentation is to look at two patient case studies and review their experience of taking an immunotherapy. The presentation will focus on how immunotherapy has impacted on their lung cancer and also on their life. As part of the patient case studies there will be a focus on the nursing role in supporting and caring for patients on immunotherapy in a safe and effective manner. The presentation will examine the main adverse event profiles of immunotherapy and how these differ to chemotherapy. The presentation will open with a brief synopsis of the mode of action of immunotherapy which is a 2 minute film. The main focus of the presentation however, will be on the patient experience and the nurses’ role. Currently in the UK there is a scarcity of information available to oncology nurses on the nursing care of patients on immune-oncology treatments. However, there are many transferable skills which can be utilised when caring and supporting patients and their carers who either about to commence on immune-oncology. According to Reiger (2003) the main area of expertise for nurses on the nursing care of patients on immune-oncology treatments. However, there are many transferable skills which can be utilised when caring and supporting patients and their carers who either about to commence on immune-oncology. According to Reiger (2003) the main area of expertise for nurses on the nursing care of patients on immune-oncology treatments.

**Keywords:** Systemic therapy, supportive care, Nursing implications

### SESSION NU04: MANAGING TOXICITY

**TUESDAY, DECEMBER 6, 2016 - 14:30-15:45**

**NU04.01 MANAGEMENT OF TOXICITIES ASSOCIATED WITH IMMUNOTHERAPY IN THE LUNG CANCER PATIENTS**

Michelle Turner
Radiation Oncology, Maryland Proton Treatment Center Affiliated with the Marlene & Stewart Greenebaum Cancer Center, Baltimore/MD/United States of America

Chronicity is a word that over the past few years has been utilized when talking about lung cancer treatments. From the developments of the TKIs in the early 2000’s to the approval of immunotherapy for lung cancer in 2015, we are seeing that progression free survival and in some instances overall survival continues to be on the rise. So what does this mean for the medical oncology community? Patients can be on therapies longer than a year and sometimes for several years. We now as providers face the challenge of becoming experts in the management of the long-term adverse effects of these drugs. Side effects of the targeted and immunotherapy drugs are not as predictable as their chemotherapy predecessors, and we are now dealing onset times ranging from days to years after beginning therapy. Immunotherapy drugs are the newest treatment craze and rightfully so, as we have seen documented 12 month overall survival in both non-squamous and squamous cell carcinoma for some of these agents and even up to 24 months for some patients. Although this has brought optimism to both providers and patients alike, it has also brought forth a multitude of side effects that remind us that we are still novices in this field and necessitate the collaboration with our non-oncologic colleagues as some of these side effects can be life-long. This lecture will review the mechanism of action of these drugs and how these differ from the chemotherapy profile. For example, patients can be on therapies longer than a year and sometimes for several years. Therefore, it is crucial to ensure that patients and their carers have a good understanding of the potential side effects and how these may affect their everyday life. This lecture will also focus on the role of the Clinical Nurse Specialist in providing education and support to patients and their carers. The presentation will be a focus on the nursing role in supporting and caring for patients on immunotherapy in a safe and effective manner. The presentation will examine the main adverse event profiles of immunotherapy and how these differ to chemotherapy. The presentation will open with a brief synopsis of the mode of action of immunotherapy which is a 2 minute film. The main focus of the presentation however, will be on the patient experience and the nurses’ role. Currently in the UK there is a scarcity of information available to oncology nurses on the nursing care of patients on immune-oncology treatments. However, there are many transferable skills which can be utilised when caring and supporting patients and their carers who either about to commence on immune-oncology. According to Reiger (2003) the main area of expertise for nurses on the nursing care of patients on immune-oncology treatments.

**Keywords:** Chronicity, immunotherapy, lung cancer

**NU04.02 EXPERIENCE OF LUNG CANCER PATIENTS RECEIVING IMMUNOTHERAPY**

Rachel Thomas
Palliative Care, Guy’s and St Thomas’ NHS Trust, London/United Kingdom

With the emergence of immunotherapy in lung cancer, patients now have access to treatments that have the potential to improve prognosis. Patients

**Keywords:** Chronicity, immunotherapy, lung cancer

**NU04.03 WHERE ARE WE WITH TKI TOXICITIES**

Beth Eaby-Sandy
Abramson Cancer Center, Hospital of the University of Pennsylvania, Philadelphia/PA/United States of America

Thoracic oncology nursing is now entering over 10 years of experience with managing EGFR and ERBB2 kinase inhibitor (TKI) toxicities, most notably epidermal growth factor receptor (EGFR) inhibitor associated rash. The three approved EGFR inhibitors used to treat non-small cell lung cancer (NSCLC) are afatinib, erlotinib, and gefitinib. Most recently, the drug Osimertinib, for EGFR mutation resistance known as T790M, has now been approved for use. Grading of the EGFRi rash has been difficult due to its inconsistent nature in comparison to non-EGFRi rashes in the general medical community and other oncologic rashes. Consensus guidelines for the management of

**Keywords:** Immunotherapy, patient experience, nursing care
EGFR inhibitor associated rash have been produced and disseminated in the oncology community. There is a correlation between EGFRi rash and overall survival in NSCLC patients, making it imperative to keep patients with rash on the EGFRi therapy. It remains a challenge for oncology nurses to understand and manage this sometimes severe rash (see figure 1). Figure 1. Other cutaneous toxicities such as scalp rash, paronychia, hypertrichosis-namely trichomegaly (see figure 2), fissuring, pruritus, and xerosis have all been reported. The Multinational Association for the Supportive Care in Cancer (MASCC) has produced recommendations for these toxicities as well.

While they are often a minor annoyance, they can sometimes also become severe and cause dose reductions and a significant impact on activities of daily living (ADL's). Identification, prevention, and management are important tasks for oncology nurses to master to allow patients to remain on therapy. Figure 2. Other classes of TKI toxicities include the Anaplastic Leukemia Kinase (ALK) inhibitors, where there are currently 3 drugs approved for use, alectinib, ceritinib, and crizotinib. Each of the ALK inhibitors carries different yet important toxicities, ranging from nausea/vomiting, diarrhea, edema, bradycardia, pneumonitis, myalgias with elevated CPK levels, and hepatoxicity. Whether TKI's are in development for potential use in lung cancer, such as HER2 inhibitors, BRAF inhibitors, and drugs targeting pathways dealing with RET, MET and KRAS (see table 1).

**Avant:** Lung cancer, the most common cause of cancer-related death in men and women, is responsible for 1.3 million deaths worldwide annually. Lung cancer (LC) patients face many symptoms throughout the course of their disease and these often co-occur. Among the most prevalent (ranging from 21–90%), burdening and debilitating symptoms that patients face is dyspnea. Although this symptom tends to become more frequent and persistent towards end-of-life, evidence show that even in early stage NSCLC patients who are most likely to be cured can also be faced with debilitating symptoms of dyspnea in poor QOL during survivorship (Sarna et al 2008). Dyspnea in the setting of lung cancer has a complex aetiology that includes: direct involvement of lung tissue by cancer, indirect respiratory complications related to the cancer, treatment related complications (fibrosis secondary to chemotherapy or radiation), respiratory co-morbidities (pulmonary or other co-morbid conditions (i.e. COPD) (Kvale et al 2007). Due to its complex aetiology, dyspnea also has a multimodal management strategy including both pharmacological and non-pharmacological interventions (Kloke & Cherry 2015). Pharmacological management options include bronchodilators, corticosteroids, anxiolytics, antidepressants, opioids and opioids (Ferrucci et al 2011; Kloke & Cherry 2015). The non-pharmacological interventions include patient’s education on measures for ameliorating the symptom, such as opening windows, using small ventilators, adequate positioning, respiratory training and relaxation techniques (Galbraith et al 2010; Molassiotis et al 2015). A non-pharmacological intervention that has been widely used for the management of respiratory symptoms in asthma and COPD but not lung cancer is Inspiratory Muscle Training (IMT). This method can reduce dyspnea mainly through two distinct ways. Firstly, by strengthening the inspiratory muscles therefore lessening the effort during a given task (dyspnea) and secondly by providing a means for controlled breathing. An improved inspiratory muscle strength and endurance can lead to the better management of dyspnea and therefore facilitate the increase in the level of activity and improving the quality of life for patients. Despite the wealth of data on the effect of IMT on inspiratory muscle strength and endurance, exercise capacity, dyspnea and quality of life for adults with COPD, there are no available data for lung cancer patients. Whilst the literature shows that COPD and lung cancer are correlated (Seik et al 2012), this is not sufficient to advocate towards the use of IMT in lung cancer patients experiencing dyspnea. Despite the scarcity of evidence, the fact that both COPD and lung cancer patients face many common problems such as increased resistance to airflow, air trapping and hyperventilation of the lung, increases the likelihood that IMT can also have a positive effect on lung cancer patients’ dyspnea. Aim: This randomised study aimed to assess the feasibility and effectiveness of inspiratory muscle training in patients with lung cancer regarding their dyspnea, psychological distress and quality of life. Design: The trial is a two-arm, non-blinded, randomised controlled, proof-of-principle study. Patients were randomly assigned to IMT or a control group. The IMT group received standard care and additionally included inspiratory muscle training, instructed at home follow-up every month for 3 months. Patients were recruited from the outpatient’s clinics of two large cancer centres in the UK and one in Cyprus. Participants were eligible if they a) were adults with histological diagnosis of primary LCR or mesothelioma; b) had refractory dyspnoea not responding to standard treatment for the past 2 weeks (breathlessness daily for 3 months at rest or on minimal exertion where contributing causes have been treated maximally); c) expected prognosis of <3 months as judged by the clinicians and d) had oxygen saturation above 85% at rest. Patients were excluded if they suffered from unstable COPD with frequent or acute exacerbations, had rapidly worsening dyspnoea requiring urgent medical intervention, had palliative radiotherapy to the chest received within 4 weeks or chemotherapy within 2 weeks, they were experiencing intractable cough, and those having unstable angina or clinically significant pleural effusion needing drainage. Intervention: A pressure threshold device was used to deliver IMT, which controls a constant inspiratory pressure and a zero expiratory pressure that is maintained unless the patient drastically alters his/her breathing pattern. Based on the literature on COPD patients, the intervention protocol included five sessions weekly for 12 weeks for 30 mins/day, divided over two sessions (the actual intervention had duration of 3-5 min for each session) and progressively the time was increased to 30min(s)/day. The IMT resistance level was set to a low level (baseline) that allowed the patient to inhale comfortably. Progressively, the resistance level was increased according to the patient’s performance. Outcome measures: Outcome measures were collected at baseline and monthly for 3 months, and included: physiological parameters (FEV1, FVC); perceived severity of breathlessness using six 10-point NRS; modified Borg Scale; quality of life using the short form Chronic Respiratory Disease Questionnaire; Hospital Anxiety and Depression Scale, and safety. Results: The final sample included 46 patients (M=37; F=9) at a mean age of 69.5 years old and a mean of 16 months post-diagnosis mainly with NSCLC and advanced disease (70%). Statistical and clinically important differences were seen with regard to distress from breathlessness (p=0.03), ability to cope with breathlessness (p=0.01), satisfaction with breathlessness management (p=0.001), fatigue (p=0.005), emotional function (p=0.01), breathlessness mastery (p=0.015) and depression (p=0.028). Changes were

**SESSION NU05: SURVIVORSHIP**

**Wednesday, December 7, 2016, 14:30-15:45**

**NU05.01 USE OF INSPRIMARY MUSCLE TRAINING IN MANAGING DYSPNEA IN LUNG CANCER PATIENTS**

Andreas Charalambous1, Alexander Molassiotis1, Yvonne Summers1, Zoe Stamatakzi1, Paul Taylor1,2

1Nursing, Cyprus University of Technology, Limassol/Cyprus; 2School of Nursing, Kowloon/Hong Kong Prc, 3The Christie's NHS Foundation Hospital, Manchester/United Kingdom, 4University Hospitals of South Manchester NHS Trust, Manchester/United Kingdom

**Aim:**

This randomised study aimed to assess the feasibility and effectiveness of inspiratory muscle training in patients with lung cancer regarding their dyspnea, psychological distress and quality of life. Design: The trial is a two-arm, non-blinded, randomised controlled, proof-of-principle study. Participants were eligible if they a) were adults with histological diagnosis of primary LCR or mesothelioma; b) had refractory dyspnoea not responding to standard treatment for the past 2 weeks (breathlessness daily for 3 months at rest or on minimal exertion where contributing causes have been treated maximally); c) expected prognosis of <3 months as judged by the clinicians and d) had oxygen saturation above 85% at rest. Patients were excluded if they suffered from unstable COPD with frequent or acute exacerbations, had rapidly worsening dyspnoea requiring urgent medical intervention, received palliative radiotherapy to the chest received within 4 weeks or chemotherapy within 2 weeks, they were experiencing intractable cough, and those having unstable angina or clinically significant pleural effusion needing drainage. Intervention: A pressure threshold device was used to deliver IMT, which controls a constant inspiratory pressure and a zero expiratory pressure that is maintained unless the patient drastically alters his/her breathing pattern. Based on the literature on COPD patients, the intervention protocol included five sessions weekly for 12 weeks for 30 mins/day, divided over two sessions (the actual intervention had duration of 3-5 min for each session) and progressively the time was increased to 30min(s)/day. The IMT resistance level was set to a low level (baseline) that allowed the patient to inhale comfortably. Progressively, the resistance level was increased according to the patient’s performance. Outcome measures: Outcome measures were collected at baseline and monthly for 3 months, and included: physiological parameters (FEV1, FVC); perceived severity of breathlessness using six 10-point NRS; modified Borg Scale; quality of life using the short form Chronic Respiratory Disease Questionnaire; Hospital Anxiety and Depression Scale, and safety. Results: The final sample included 46 patients (M=37; F=9) at a mean age of 69.5 years old and a mean of 16 months post-diagnosis mainly with NSCLC and advanced disease (70%). Statistical and clinically important differences were seen with regard to distress from breathlessness (p=0.03), ability to cope with breathlessness (p=0.01), satisfaction with breathlessness management (p=0.001), fatigue (p=0.005), emotional function (p=0.01), breathlessness mastery (p=0.015) and depression (p=0.028). Changes were

Keywords: Inspiratory muscle training, Integrative medicine, lung cancer, dyspnoea
Abstracts

PA01.01 THE IMPORTANCE OF PATIENT ACCESS TO MOLECULAR TESTING AND NOVEL THERAPIES
Janet Freeman-Daly
Lung Cancer Patient Advocacy, #lcsm Chat (Lcsm = Lung Cancer Social Media), Federal Way/WA/United States of America

Advances in lung cancer diagnosis and treatment are enabling many metastatic cancer patients to live months or years longer than ever before. Best practices in lung cancer detection, diagnosis, and treatment are changing so fast that keeping current with new developments is difficult for many healthcare providers—more new drugs have been approved for lung cancer in the past five years than in the previous five decades. While testing for useful biomarkers such as EGFR, ALK and ROS1 is becoming more common, such tests are not yet standard procedure in many settings. Some patients who have limited tissue or who are interested in pursuing clinical trials might benefit from liquid biopsies or next generation sequencing (NGS) panels, but such tests might not be available to them for a variety of reasons: the healthcare provider may be unfamiliar with the test or unconvincing of its merits, the facility may not have the technology or expertise to conduct the testing, or insurance may not cover the test. Even if the testing finds an actionable biomarker, patients may have difficulty obtaining novel therapies if those therapies are not approved or covered by insurance, or they may have trouble identifying and accessing appropriate clinical trials. Some biomarkers, such as PD-L1, are also less ‘definitive’ or standardized than others. This presentation discusses ways that patient access to molecular testing and novel therapies can not only improve lung cancer outcomes, but also help engage patients as partners in their own care and accelerate research through patient-driven data sharing.

Keywords: biomarkers, patient access, data sharing, novel therapies

PA01.02 THE ROUTE TO DIAGNOSIS: IMPACTING SURVIVAL BY CHANGING THE SYSTEM
Thomas Newsom-Davis
Chelsea and Westminster NHS Foundation Trust, London/United Kingdom

A significant proportion of lung cancer patients are first diagnosed with their disease as part of an emergency presentation (EP) to acute medical services. EP includes patients attending the emergency department (ED), primary care referrals to acute services, and emergency admissions to secondary care. This route to diagnosis is more common in lung cancer than other malignancies1. Initial studies focused on the United Kingdom, where 40% of lung cancer patients were found to present in this fashion1, but it occurs in all European countries, with rates up to 52%2. Lung cancer patients presenting via EP tend to be older, have lower socio-economic status and greater social deprivation, display worse overall health, and have a lower performance status3. They are more likely to present with advanced stage disease and are less likely to have surgery or other treatments with curative intent4. The emergency route to diagnosis is associated with poorer patient experience and is a significant additional burden on acute medical services5. Most importantly, EP lung cancer patients have poorer survival6, the risk of dying in the first month post-diagnosis is four times higher for EP compared to non-EP patients7. For the majority of lung cancer patients, there are opportunities for earlier diagnosis and prevention of EP8. Most have a relatively long history of symptoms, often more than 12 weeks, and three-quarters have been to their general practitioner (GP) with their symptoms, usually on several occasions. There is also a group of patients who delay consulting a doctor, and they are more likely to report barriers to presenting to healthcare services9. Novel methods of lung cancer diagnosis, focusing on symptom recognition, early involvement of primary care and prompt assessment in secondary care, have the potential to address this important problem. In the UK, the issue of late diagnosis and EP of cancer is increasingly recognised in cancer strategies. A number of innovative approaches have been brought together by the ACE (Accelerate, Coordinate and Evaluate) program, which aims to improve early diagnosis of cancer across a range of tumour types by learning from current best-practice and trialling new projects, many of which focus on lung cancer10. These are now informing health policy. Prominent independent reports have also addressed the EP of lung cancer, and have produced a series of recommendations11. At a national level, campaigns to raise public awareness of the signs and symptoms of lung cancer can help promote earlier presentation to primary care, whilst the adoption of lung cancer screening programmes has the potential to reduce the number of lung cancer patients diagnosed late. Lung cancer risk assessment and clinical decision support tools can assist the GP. System-based tools use patients’ current symptoms to provide an indication as to who should be referred for further investigations, whilst lung cancer risk prediction models identify high risk individuals without symptoms for CT screening. These require further testing and validation, but if proven successful, should be added into primary care pathways. Other approaches have pioneered open-access patient self-referral for chest radiographs. The ED is often used as a safe and quick access point to secondary care, even for those patients who do not require emergency medical care. Developing new outpatient pathways can prevent EP by providing GPs with access to rapid-access clinics for patients with, for example, clinical suspicion of cancer but who are too unwell to wait 2 weeks for an urgent outpatient appointment, or those in whom the likely tumour type is not clear12. The Danish pathway for patients with serious but non-specific symptoms and signs of cancer is an international example13. To support the patient through their whole journey and expedite the diagnostic process, a clinical nurse specialist (CNS) should be available to all patients undergoing investigations for suspected lung cancer. Those who present via EP should be seen within 24 hours by a CNS who then acts as their key worker. The patient should be registered on a hospital card, so that diagnosis and EP can be held together. The Danish patient is afforded the same treatment opportunities as those presenting via elective routes. Although there is not one solution to the problem of EP in lung cancer, and different approaches are needed for different health systems, there are common themes by which survival can be improved by changing the system for the patient group at risk. The ACE program has shown that practice change can be achieved at scale providing the opportunity to change the system for this vulnerable patient group.


Keywords: Emergency, Presentation, Routes, diagnosis

PA01.03 ESTABLISHING A PARADIGM FOR HIGH QUALITY LUNG CANCER TREATMENT
David Leduc
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Due to the complexities of diagnosing and treating lung cancer, and the high mortality rate of the disease, lung cancer specialty centers are more common than ever. Proper and timely diagnosis and development of a patient-specific treatment plan can impact patient outcome and quality of life with vulnerable populations, such as those who are uninsured or who live in rural and remote places, often not having access to the quality of care and multi-disciplinary approach to treatment found in specialty centers. This dynamic results in vulnerable populations being diagnosed in later stages, with limited treatment options and poorer outcomes than those patients with access to quality multi-disciplinary care. The Addario Lung Cancer Foundation (ALCF) Community Hospital Center of Excellence Program (CEP) directly addresses this need by partnering with community hospitals, where 80% of cancer patients are treated, to deliver standard of care lung cancer screening,
is rare, nationally and internationally. In response to the need to improve national lung cancer services, Lung Foundation Australia (LFA) successfully secured funding through the Cancer Australia grant initiative “Supporting people with cancer”. LFA directed these funds toward addressing challenges identified by Cancer Australia within the lung cancer community through the appointment of a Lung Cancer Nurse to provide support and information across all stages of a lung cancer patient’s experience – not only at diagnosis, but also as a consistent point of contact throughout an extremely stressful and uncertain time. The service is intended to be a vital link in delivering health services, supporting both patient and carer throughout their journey. The role of the LFA Lung cancer nurse has evolved with the launch of the National Lung Multidisciplinary Team (MDT) directory in June 2016. This directory, currently representing 64 Lung MDTs, provides a detailed understanding of the services each hospital can provide for a patient, from diagnostics through to various treatment modalities. These two key initiatives - the Lung Cancer Nurse Service and National Lung MDT Directory - have become intertwined, supporting the needs of patients and, importantly, navigating them towards achieving the best level of care whilst ensuring the patient, their family and carers feel supported, informed and respected. The most significant aspect of the Lung Cancer Nurse Service is that of patient advocate, reflecting and representing the needs of patients nationally and, where appropriate, linking patients back into the healthcare system. Lung cancer specialist nurse roles are pivotal in representing lung cancer patients, improving access to new diagnostic technologies and tests, clinical trials, symptom management, access to community based support, education and empowerment. Lung cancer patients need a service that is accessible, patient driven and provides an individualized service. The Lung Cancer Nurse Service is dedicated to providing a comprehensive, patient and carer centered service that is available in all areas of the community. The Lung Cancer Nurse Service is a vital link in delivering efficient, up-to-date information for patients and carers seeking support and guidance. Ultimately the objective of the Lung Cancer Nurse Service is to continue to address the principles of best practice management in lung cancer ensuring; the patient and carer feel supported, informed and respected; all patients receive timely access to all components of their care regardless of location; and patients have access to all relevant treatment and supportive options, including early enrolment into coordinated lung cancer care. This Service complements the support structures that are already in place, so clinicians can continue to strive to ensure the needs of lung cancer patients can be addressed and increase much-needed support and resources. The experience in establishing this new role within LFA, forming collaborations with national Lung Cancer MDTs and the measurable impact of the role on outcomes for lung cancer patients, will be presented in both qualitative and quantitative terms. Keywords: Lung cancer support nurse, Telephonic support, Multidisciplinary Team Directory

**PA01: LUNG CANCER MANAGEMENT IN TURKEY**
Seda Kansu1, Beril Koparal1, Lutfi Kirdar3, Hasan Batireli2, Roza Çetinöz2, Ahmet Ozet3

1Pembe Hanım, Istanbul/Turkey, 2Training and Research Hospital Department of Oncology, Istanbul/Turkey, 3Department of Thoracic Surgery, Marmara University Medical Facult, Istanbul/Turkey, 4Medical Oncology, Istanbul University, Istanbul/Turkey, 5Turkish Medical Oncology Society, Istanbul/Turkey

The incidence of cancer in Turkey is 267 and 186 in a hundred thousand in men and women respectively. Lung cancer is the number one cause of cancer death in men in Turkey and its incidence is increasing in women in recent years as well. It is the fifth common cause cancer after breast, colon, thyroid and gynecologic malignancies in women in Turkey. The number of cancer cases directly related with smoking is expected to be 31,000. The incidence of lung cancer in men and women is 21.9 and 5.3 in a hundred thousand respectively. Namely there are 50,000 lung cancer patients in Turkey. And each year a new 30,000 patients are added to this number. Between 2009-2013, the incidence of lung cancer among men has decreased from 56 to 51 in a hundred thousand. However the number has increased from 16 to 18 in a hundred thousand among women. This decrease among men is the positive result of effective smoking cessation campaigns as the main cause of lung cancer in Turkey is smoking. The second reason is air pollution in workplaces. Lung cancer is diagnosed generally at late stages in Turkey as well as in the west, and more than 50% of the patients present with metastatic disease at diagnosis.
Only minority, less than 20% present with localized disease and these cases are generally detected incidentally for other health reasons. Curative surgery can be offered to only 15% of the patients. There is no effective prevention other than smoking cessation and screening which is found more popular for certain risk groups in the west but it is not a proposed method actually in Turkey. Treatment decisions in high volume centers are taken by multidisciplinary way including radiologists, pathologists, nuclear medicine specialists, surgeons, medical and radiation oncologists. Surgery is the primary treatment modality in early stages of disease, and lung cancer surgeons are well experienced throughout the country being able perform all sort of surgical techniques including robotic one with high success. Cancer chemotherapy and radiotherapy are well developed in the country with the availability of recent FDA approved targeted drugs and immunotherapeutic agents as well. Certain centers in Turkey are also included in multinational studies involving new agents in treatment of this disease. Radiation oncology centers are equipped with high technology radiotherapy machines being able to perform image guided intensity modulated radiotherapiess and stereotactic radiotherapiess in treatment of lung cancer. For the last years prevention programs in Turkey has increased. Two main actions for this are smoking cessation and fight against air pollution. The effectiveness of early diagnosis programs in lung cancer has not been proved. There has been an initiation of screening programs by low dose CT in high-risk patients. The diagnosis and treatment of lung cancer is in line with global standards considering surgery, radiotherapy and chemotherapy. The global improvements in lung cancer is closely followed by oncologists and scientists in Turkey and rapidly integrated into clinical practice by means of prevention, diagnosis, treatment and follow-up. However the patient care in terminal stage should be improved. The set up of hospice centers has taken into consideration and targets for 2020 are the determination of molecular genetic targets for diagnosis and the treatment of lung cancer, the identification of cellular therapies and immunotherapy and other targeted therapy modalities. In Turkey it is not possible to talk about early diagnosis. But we can talk about early stage diagnosis. The rate of early stage lung cancer patients in Turkey key is less than 1%. Unfortunately population based screening programs for lung cancer has not been approved by Ministry of Health yet. With a screening program a tumor of 1 cm can be diagnosed. However a patient with symptoms being diagnosed has a tumor of 3 cm and the rate of cure between these patients is really different. S year survival for a patient with a tumor of 1cm is 100% and a patient with a tumor of 3cm is 65-70%. Under screening programs for high-risk patients, the risk of death from lung cancer decreases 20%. On the patient organization side Pembe Hanım Association has made the first attempt in Turkey to raise awareness in the public for lung cancer. For four years a Project called “MegaLung” has reached many people talking about the prevention, diagnosis, and treatment of lung cancer. This was the first and only project about lung cancer. “MegaLung” had its place in many organizations open to public to reach as many people as possible as lung cancer is a wide range cancer and it has a preventable cause namely smoking. At the moment with the collaboration of members of Pembe Hanım Association, Dr. Seda Kansu and Turkish Lung Cancer Society, a patient organization for lung cancer called “Nefes (Breath)” is being set up with the aim of raising awareness among public and lung cancer patients about the all the issues related with lung cancer. As Pembe Hanım Cancer Patients Society we would like to thank Turkish Society of Medical Oncology, Turkish Lung Cancer Society, Dr. Lutfi Kirdar Kartal Training and Research Hospital Department of Oncology and Marmara University Medical FacultyDepartment of Thoracic Surgery for their valuable support. Seda Kansu IASLC Patient Advocates Committee MemberReferences

Pembe Hanım Cancer Patients Society
Turkish Society of Medical Oncology
Turkish Lung Cancer Society
Dr Lutfi Kirdar Kartal Training and Research Hospital Department of Oncology
Marmara University Medical FacultyDepartment of Thoracic Surgery

SESSION PAO2: ACCESS TO CARE - EQUAL CHANCES IN THE WORLD?
MONDAY, DECEMBER 5, 2016 - 16:00-17:30

PAO2.01 ACCESS TO CARE: USA
Kim Norris
President, Lung Cancer Foundation of America, Marina Del Rey/CA/United States of America

In the United States of America (USA), the public is dangerously uninformed about lung cancer, our nation’s second leading cause of death behind heart disease. Lung cancer accounts for more deaths than any other cancer, more than breast, prostate and colon cancer combined. As estimated 220,000 new cases of lung cancer will be diagnosed the USA in 2016 resulting in 158,080 deaths or about 27% of all cancer deaths 2016. Ready access to effective and comprehensive medical care at a reasonable cost is the key to our well-being. This is especially true for lung cancer. For lung cancer patients, access takes many forms, to include diagnosis, treatment and financial support for care and treatment. Regardless, for lung cancer patients, time is of the essence, making quick, effective and affordable access to care critical.

This discussion will focus on four areas that affect access to care for lung cancer be it at the diagnostic stage or the treatment and care stage:

1. Stigma: At the outset, the negative bias against lung cancer may weigh against early access to treatment. 68% of advanced cancer patients who have never received cancer care are lung cancer patients. 6 Cancer patients, healthcare professionals, caregivers and the general public are all equally likely to have a negative bias toward lung cancer.

2. Timely diagnosis: The good news is that thanks to advances in technology, early detection screening using spiral CT has been shown to reduce lung cancer deaths by 16% to 20% (in a defined population), compared to standard chest x-rays among adults. Yet, only 16% of people will be diagnosed in the earliest stage, when the disease is most treatable and at best, early diagnosis is usually the serendipitous result of some other unrelated procedure. Aside from the lack of public awareness that anyone with a set of lungs may be at risk for lung cancer, there remains no standard effective diagnostic tool for lung cancer. The development of affordable diagnostic tools using biomarkers in airway epithelial cells, sputum, blood, breath, and urine for early diagnosis and prediction of high risk individuals is critical.

3. Current and evolving treatment options: Once again, the good news is that treatment options for lung cancer patients are rapidly improving. In the last two years more treatments have been approved by the United States Food and Drug Administration (FDA) for the treatment of lung cancer than had been approved in the prior ten years. Most of the discoveries and associated clinical trials are happening at academic centers yet 80% of lung cancer patients are treated at their local community hospital. New and life savings treatments along with clinical trials are happening so quickly that it is sometimes challenging for these advancements to reach the treating physician thereby limiting ready access of these new treatments to the patient.

4. Cost of treatment and care: The Patient Protection and Affordable Care Act (PPACA), commonly called the Affordable Care Act (ACA) or Obamacare, is a United States federal statute signed into law by President Barack Obama on March 23, 2010. In April 2016, Gallup reported that the percentage of adults who were uninsured dropped from 18% in the third quarter of 2013 to 11% in the first quarter of 2016. Although individual insurance coverage has improved, the rapid pace of discovery and FDA approval of treatments, insurance paysors and federal medical care assistance programs have not necessarily kept pace with these advancements in both testing and treatments by not providing insurance coverage, leaving lung cancer patients without the financial ability to pay for needed care. Various organizations, such as ESMO, ASCO, ICER and others are attempting to compare drug prices to overall patient benefit through programmed algorithms in order to assist paysors and patients in treatment decision making. These are often long and laborious projects which may be out of date by the time the recommendations are published, and impede quick access to treatment and care Patients and patient advocates are in a strategically advantageous position to affect change in these four areas in order to provide greater access to care for all lung cancer patients. 1 http://www.medicalnewstoday.com/articles/282929. php#top_10_leading_causes_of_death_in_more_detail 2 http://www.cancer.org/acs/groups/content/@editorial/documents/ document/acspc-044552.pdf 3 American Cancer Society. Cancer Facts & Figures 2016. Atlanta: American Cancer Society; 2016.


Keywords: Early Detection, patient advocacy, Cost of Care, stigma
PA02: ACCESS TO CARE: EQUAL CHANCES IN THE WORLD?
MONDAY, DECEMBER 5, 2016 - 16:00-17:30

PA02.05 ACCESS TO CARE: AUSTRALIA

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1National Lung Cancer Program, Lung Foundation Australia, Brisbane/Australia.
2Lung Cancer National Program, Lung Foundation Australia, Brisbane/Australia.

In June 2016, Lung Foundation Australia launched an evidence-based, clear and concise guide, the “Lung Cancer Patient Pathway”, for patients with a confirmed lung cancer diagnosis. The guide is available as a printed resource and online resource supported by a micro-site on Lung Foundation Australia’s website and the Lung Cancer Network Australia website. To date, the guide has been distributed to the majority of dedicated lung cancer treatment centers across Australia. Project aims: The main aim of producing the Lung Cancer Patient Pathway (LCP) was to provide newly diagnosed patients with a “one stop” resource that outlines the clinical referral pathways and details the full range of treatment options and supportive care services available to them throughout their lung cancer journey.

The LCP also aims to improve patient health literacy and empower patients with access to evidence based information to support informed decision making and treatment choices, self-management and ultimately, to improve patient outcomes. Project Synergies: The LCP was launched in conjunction with the launch of the Lung Foundation’s Australian Lung Cancer Multi-Disciplinary Team Directory (http://lungfoundation.com.au/mdt). This national directory lists the current (60) dedicated lung cancer multidisciplinary (MDT) services around Australia. It is intended to facilitate referrals of patients to hospitals delivering MDT-based lung cancer management. The creation of this national directory has forged closer relationships between the Lung Foundation and dedicated lung cancer multidisciplinary (MDT) services and provided a mechanism to be able to reach patients at time of diagnosis. Lung Foundation has previously struggled to reach patients early in their cancer journey. Strengthening these relationships with Lung MDT services has led to a systematic distribution of Lung Foundation patient kits including the LCP info-graph. The Cancer Nurses Society of Australia Winter Congress in May 2016 and Australian Lung Cancer Conference in August 2016 presented opportunities to distribute the printed LCP in conference delegate bags and at trade exhibitions to more than 550 cancer clinicians and nurses.

Sustainability: The Lung Foundation will implement the following strategies to ensure the sustainability of this project: - Info-graph will be trialled in Australia's Lung Cancer MDTs around Australia - Info-graph will form part of the Lung Foundation Consultative Groups activities - A minimum review period of two years for info-graph and website content - Annual budget allocation for ongoing promotion and dissemination

Conclusion: The Lung Cancer Patient Pathway project has produced a patient centered resource to empower newly diagnosed patients with current, evidence based information so that they can make informed decisions on treatment options and supportive care services and access the right treatment and care at the right time. This project was managed by Glenda Colburn, Director, Lung Cancer National Program, Lung Foundation Australia. The Lung Cancer patient pathway was made possible via unrestricted education grants. Principal sponsors: Bristol-Myers Squibb Supporting Sponsors: AstraZeneca, Boehringer Ingelheim, Cancer Australia, Pfizer, Maurice Blackburn Lawyers, MSD.

Keywords: Pathway, patient, lung cancer, Access

PA02: ACCESS TO CARE: EQUAL CHANCES IN THE WORLD?
MONDAY, DECEMBER 5, 2016 - 16:00-17:30

PA02.06 ACCESS TO CARE: ISRAEL

Shani Shilo

The Israel Lung Cancer Foundation, Rehovot/Israel

The defining characteristic of the health system in Israel is its governance by the National Health Insurance Law (1995). This law ensures health coverage to every resident of Israel and defines the government’s responsibility to provide health services to every person without discrimination. In other words, health insurance is mandatory, and all residents of Israel must be insured. Citizens pay a healthcare tax - 4.8% of income. Private Health Services Patients have the option of seeking private medical care from a physician of their choice, and at their own expense. There are four health funds, where each fund has branches throughout the country and provide its members with all mandated services. The Basket of Health Services, consists of a range of essential medical services, including treatments, medications, and equipment which each health fund is obligated to provide to its members. Its contents are defined by law, but are subject to periodic revision. Therefore, a treatment or medication that was covered at one point may be discontinued, or new items may be added. Every end of a year, new treatments and technologies are submitted to be included to the new health basket. First the physicians rate the proposed new treatments and technologies, then the top ones enter the basket debate, where eventually only some every year enter the health system. In the past years, new expensive treatments and technologies could enter the basket only until the sum of 300 million NIS, that equals, 80 million dollars. This year the basket fund was increased to 146 million dollars. The problem is that there are many new treatments and that the oncology rating is among all oncological diseases. Last year, four new lung cancer drugs were proposed to the health basket. The Israel Lung Cancer Foundation, advocated in the Israeli Knesset (house of parliament), attended meetings, raised awareness in digital and written media. Eventually 3 new lung cancer drugs were approved including OPDIVO, TAGRISSO and ALECTINIB. This end of year, KYTRUDA and ODPIVO
SESSION PA03: PATIENT SUPPORT AND INVOLVEMENT IN RESEARCH TUESDAY, DECEMBER 6, 2016 - 11:00-12:30

PA03.01 ESTABLISHING A CENTRAL EUROPEAN LUNG CANCER PATIENT NETWORK
Franz Buchberger
Lungenkrebsforum Austria, Himberg/Austria

Background: Patient Advocacy Groups (PAG) can improve the situation of lung cancer patients by participation as stake-holders in decision processes, by building awareness for the disease and by lobbying at politicians.

As a matter of fact there are existing European patient advocacy networks for different kinds of cancer, e.g. breast cancer, prostate cancer etc. working strongly and successfully together i.e. building awareness for these diseases. Although lung cancer is one of the most common types of cancer worldwide there is a lack in patient advocacy groups created by a shorter live time of lung cancer patients compared with other patients.

While there are national LC patient advocacy groups in almost every country of Western Europe they are very rare in Eastern European countries and consequently need special attention. This project was motivated by the break-out session during the “Central European Initiative Against Lung Cancer” in 2014. The main results requesting from the expert discussion included that lung cancer patients need to speak up and international PAGs should be connected with each other. The Austrian LC patient advocacy group, Lungenkrebsforum Austria, initiated the Central European Lung Cancer Patient Network and started with the first steering committee meeting in July 2014. Medical experts from Austria, Czech Republic, Hungary, Slovakia and Slovenia determined the aims of CELCAPANET with promotion and support of PAG establishment, providing a network for PAG within Central Europe and empowering patients. Challenged by the fact that all potential patient organizations had to be contacted and engaged to participate in the newly formed project the first patient advocacy meeting was held in November 2014 with participating general oncological PAG from Croatia, Hungary, Poland, Slovakia and Slovenia. One of the main outcomes of this meeting was the mandatory participation of all three fields where the peer support programmes have been found to be applicable: 1) social and also health providers. The programme is carried out through recognized professionals and in understanding coping processes. The programmes main goal is to inform participants on the lung cancer diagnostics, treatment and the rehabilitation possibilities. This information is given by the relevant professional. There is a special emphasis on the new and more efficient treatment possibilities. The programme presents in program participants the treatment possibilities and the mean for the optimal coping with the disease and its treatment and also the advice for the living with the disease. We are widening the importance of comprehensive patient treatment, informing on psycho social considerations, possibilities on entering the CPAS programmes (and also related programmes that are offered locally), we are informing on benefits of early inclusion in the palliative care thus butting the myths regarding the palliative care. Except for presenting information, the programme’s goal is also the social support for lung cancer patients, as a large amount of the time is set by focus group and the exchange of experiences among the participants. Inclusion of different professional groups into the programme is important for lung cancer patients due to the patients’ needs is being represented on the symbolic level with the joint presentation, where the presenters are alternating thus rounding up the “story” of treatment and rehabilitation. Incorporated in the programme is also a chance for the patients and their families to have an individual conversation with the medical professionals regarding their treatment and dilemmas. While the programme is being primarily aimed at the patients and their relatives, the local medical professionals are also invited. This beside the information point of view gives them also a chance to interact with the presenters and an opportunity to discuss with them their questions and dilemmas. Through this we are trying to ensure the equal availability of treatment and to approach the people with medical and psychosocial support. Conclusions: With this programme we are following all three fields where the peer support programmes have been found to be beneficial to patient. Namely needs around the lung cancer and its treatment, management of emotional distress and finally the facilitation of empowerment. 


PA03.03 HOW TO LIVE WITH LUNG CANCER? THE SLOVENIAN LUNG CANCER PATIENT SUPPORT
Andrea Cirila Škufca Smrdel
Dept. of Psycho-Oncology, Institute of Oncology Ljubljana, 1Cancer Patients’ Association of Slovenia, Ljubljana/Slovenia

Background: Cancer Patient’s Association of Slovenia (CPAS) is a non-governmental organisation, connecting the patients with all cancer types as well as their relatives and health professionals. The central programme that is being offered to patients by CPAS for more than three decades is an organized self-help «on the way to recovery», that offers support in self-help groups on 20 locations and peer-to-peer counselling in two Info centres. The lung cancer patients are entering the programme alongside the other cancer patients. The peer-to-peer support programme has developed the system of regular supervisions, initial education, the study material aimed at volunteers and the network of self-help groups spread over the Slovenia. The research analysing peer-to-peer support showed clear benefits for the patients1-3. Since 2014, the Lung Cancer Support Division is organised in the framework of CPAS. Its main aim is the development of the programmes for lung cancer patients and their relatives. In Slovenia, with roughly 2 million inhabitants, there are approximately 1230 new lung cancer patients every year, and 1100 deaths due to lung cancer2. Patients with lung cancer are treated in four oncological centres (Institute of Oncology Ljubljana, University Clinic Golnik, University Medical Centres Ljubljana and Maribor). Among the burdens, all cancer patients are carrying, such as confronting its own vulnerability, mortality, coping with the apprehensions of treatment, psychic distress often combined with the fear of recurrence, lack of social support and changes in financial situation, some are disease specific. The burdens lung cancer patients are experiencing are connected with the poor prognosis, poorer quality of life and greater symptom management needs. These are due to physical troubles, social pressation of lung cancer as death sentence, sense of guilt and stigmatisation, but are also due to the need of information regarding new treatments available4-5. To be able to react on the specific lung cancer patient’s needs, we have within the Lung Cancer Support Division supplemented volunteer self-help programme «on the way to recovery».

The European Medicines Agency (EMA) is the authority which evaluates and monitors medicines across all EU Member States. Pharmaceutical companies wishing to market a new cancer medicine in Europe are obliged to apply for a licence through the EMA. With a remit to ensure that European citizens are provided with safe and effective medicines, the EMA realised early on that patients’ experience with their disease and its treatment is a fundamental parameter to include within the evaluation of medicines. The Agency’s engagement with these stakeholders has been a progressive journey whereby a steady increase in the numbers involved (76 in 2007 to 740 during 2015) has been coupled with a diversification of methodologies ensuring opportunities all along the medicines lifecycle. Learning from experience has also been paramount to ensure that the interaction is mutually beneficial and is carried out in the most optimal manner possible. Key milestones of EMA interaction with patients and consumers:

1. **A forum of exchange: EMA Working Party with Patients and Consumers’ organisations**
   - Awareness campaigns, roundtables, conferences
   - Discussion on benefit/risk evaluations
   - Scientific advice procedures during medicines development

2. **Interaction with the EU Regulatory Network**
   - Scientific advice procedures during medicines development
   - Discussions on benefit/risk evaluations
   - Review of information (e.g. package leaflet, safety communication)

3. **Capacity-building focusing on training and raising awareness about EU regulatory system**
   - Education and awareness programmes

4. **Today patients and consumers are systematically involved in a wide range of EMA activities:**
   - Members of EMA Management Board and scientific committees
   - Members of the EMA ‘Patients and Consumers Working Party’
   - Discussion on benefit/risk evaluations
   - Review of information (e.g. package leaflet, safety communication)

The “framework of interaction” adopted by the EMA management board in 2005 provides the formal basis for involving patients and consumers in Agency activities and relies on five critical elements:

- A network of European patients and consumers organisations
- A forum of exchange: EMA Working Party with Patients and Consumers’ organisations
- A pool of patients acting as experts in their disease and its management
- Interaction with the EU Regulatory Network
- Capacity-building focusing on training and raising awareness about EU regulatory system

Today patients and consumers are systematically involved in a wide range of EMA activities:

- Members of EMA Management Board and scientific committees
- Members of the EMA ‘Patients and Consumers Working Party’
- Scientific advice procedures during medicines development
- Discussions on benefit/risk evaluations
- Review of information (e.g. package leaflet, safety communication)

The Agency works with a large network of organisations and individuals; organisations can register with the Agency and if they meet certain eligibility criteria they are then listed on the EMA website (EMA website). Individuals are also encouraged to register to be included in the EMA “individual experts’ stakeholder database” (registration form); they then receive targeted information and can be contacted for involvement in EMA activities. Patients usually participate in person or via written procedure and are involved as either representatives of their organisation or as individual experts, depending on the nature of the activity. There are opportunities for involvement all along the medicine’s evaluation lifecycle:

- **Today patients and consumers are a valued and integral part of the work at the EMA and their perspectives are considered an essential element for increasing transparency in the regulatory process and ensuring more meaningful decisions for all concerned.**

**Keywords:** patient support, non-governmental patient organization, lung cancer

**PA04.01 A REALISTIC GOAL? ACHIEVING A TOBACCO FREE IRELAND BY 2025**

Donal Buggy
Head of Services & Advocacy, Irish Cancer Society, Dublin/Ireland

**Introduction:** Ireland has a proud record of leadership in the field of tobacco control. It was the first country in the world to introduce a Workplace Smoking Ban in 2013 and the first country in Europe to announce its intention to introduce plain packaging for cigarettes. In 2013 Ireland set a target date to achieve a tobacco free society with a targeted adult tobacco use prevalence of under 5%. Other countries to formally adopt a target for tobacco free societies include Finland 2040, New Zealand 2025, and Scotland 2034. Tobacco Free Ireland is a new tobacco policy for Ireland coming more than a decade after the publication of the previous national policy Towards a Tobacco Free Society 1. It is a timely successor because of the emerging non-communicable disease burden which is caused by risk factors that can be prevented. Tobacco is well known as a major contributor to ill-health and premature mortality. It is responsible for more than a third of all cancers. For the first time, we have a target date for Ireland to be tobacco free of 2025. The question is whether this target is in any way realistic.

**Discussion:** Tobacco Free Ireland addresses a range of tobacco control issues and initiatives and contains over 60 recommendations. A high level action plan, was drawn up in consultation with those who will lead out on the recommendations which outlines the responsibilities, actions necessary and timelines for the implementation of the recommendations. The recommendations to support Ireland becoming a tobacco free Society are categorised under:

- Protection of children and denormalisation of tobacco use
- Increase the dissemination of EMA outcomes
- Increases the quality of patient information and communication on medicines
- Today patients and consumers are a valued and integral part of the work at the EMA and their perspectives are considered an essential element for increasing transparency in the regulatory process and ensuring more meaningful decisions for all concerned.

**Keywords:** patient engagement

**SESSION PA04: FOCUS ON ADVOCACY AND COMMUNICATION: JOINT IASLC/ GLOBAL LUNG CANCER COALITION SESSION (GLCC)**

**TUESDAY, DECEMBER 6, 2016 - 14:30-15:45**
Background: The Global Lung Cancer Coalition (GLCC) is a unique partnership, dedicated to improving disease outcomes for all lung cancer patients worldwide. Research is essential to drive improvements in cancer prevention, screening, diagnosis and treatment. However, it is clear that lung cancer research is not being prioritised to a level that reflects its significant impact, with 1.8 million new cases globally every year.

We Can Quit programme, which challenges intergenerational smoking, have been successful and need to be funded and enhanced if a Tobacco Free Society is to be achieved. Conclusion: Current adult smoking rates of 19.5% suggest Ireland has some significant way to go towards achieving its target. Recent youth smoking rates of 13% for 15-17 year olds and 8% for 10-17 year olds suggest significant progress in reducing the uptake of smoking. Major investment is required to support increased quit attempts and increased success from quit attempts if the target of a Tobacco Free Ireland by 2025 is to be achieved.


Keywords: tobacco policy, smoking inequalities

PA04.02 THE GLOBAL STATE OF LUNG CANCER RESEARCH – COMMUNICATING THE MESSAGES

Sarah Winstone
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Background: The Global Lung Cancer Coalition (GLCC) is a unique partnership, dedicated to improving disease outcomes for all lung cancer patients worldwide. Research is essential to drive improvements in cancer prevention, screening, diagnosis and treatment. However, it is clear that lung cancer research is not being prioritised to a level that reflects its significant impact, with 1.8 million new cases globally every year. Poor lung cancer survival demonstrates that more can and should be done. The GLCC is calling for every country across the globe to examine and increase its investment in lung cancer research. Evidence of variations between countries in their approach to lung cancer research can be a powerful tool to advocate for increased investment and national policy that encourages a flourishing lung cancer research community. The GLCC commissioned the Institute of Cancer Policy at King’s College London to undertake a comprehensive examination of the state of global lung cancer research. The findings, published in the Journal of Thoracic Oncology, are intended to guide public policy and highlight where improvements can and should be made. They have also been made available on the GLCC website with a range of campaigning materials for advocates to use in sharing insights and recommendations. Methodology: The GLCC commissioned the Institute of Cancer Policy at King’s College London to undertake a bibliometric review of global lung cancer research efforts. The team developed a complex validated mathematical algorithm to search articles and reviews in the Web of Science database for lung cancer research during 2004-13, looking to: Identify the total number of papers in cancer research for each year in 24 leading countries, compared to that of other common cancers (breast and colorectal) - Isolate the number of papers referencing lung cancer or other relevant key words in their title The study identified the 24 countries globally with the most extensive research programmes in lung cancer. The authors’ research institutes were used to identify which country or countries had contributed to that paper. The study also analysed whether research outputs had changed over time as well as the focus of the research and how close the research is to patients. The methodology allows total number of papers, type, and research collaborations to be analysed over time. Results: The bibliometric review is a comprehensive and powerful resource allowing lung cancer patients, clinicians and policymakers to examine their national lung cancer research output and compare it with that of other countries. The 24 countries responsible for the majority of lung cancer research activity are: Australia, Austria, Belgium, Brazil, Canada, China (People’s Republic of), Denmark, France, Germany, Greece, India, Italy, Japan, Netherlands, Norway, Poland, Taiwan, Turkey, South Korea, Spain, Sweden, Switzerland, United Kingdom, and the USA (figure 1).

Worldwide, the number of papers published on lung cancer has more than doubled from 2,157 papers in 2004 to 4,845 in 2013. However, there has only been a small increase in the proportion of global cancer research that is dedicated to lung cancer – from 4.4% in 2004 to 5.6% in 2013. By comparison (figure 2), both breast and colorectal cancer account for greater proportion of research activity, despite having a similar burden of disease.

Colorectal cancer accounted for 6.2% of research activity in 2013 whereas breast cancer, at 10%, had nearly double the percentage of research activity compared to lung cancer. The figures can be used to make a persuasive case for increased investment in lung cancer research. To support this, the project team produced a campaigning toolkit, giving headline figures and statistics, tips for engagement and template briefings and press releases. Global and national-level briefing documents and infographics are also available on the GLCC’s website at: http://www.lungcancercoalition.org/en/state-global-lung-cancer-research. The GLCC is calling for every country across the globe to increase its investment in lung cancer research, to increase research efforts in aspects of care that are currently under-researched, and to collaborate with international partners to share findings and improve patient care.

**Keywords:** campaigning, bibliometric, global lung cancer research, advocacy

PA04: FOCUS ON ADVOCACY AND COMMUNICATION: JOINT IASLC/GLOBAL LUNG CANCER COALITION SESSION (GLCC)

TUESDAY, DECEMBER 6, 2016 - 14:30-15:45

PA04.03 HELPLINE: ADAPTING TO CHANGING NEEDS AND EVOLVING SCIENCE

Jennifer King

Science & Research, Lung Cancer Alliance, Washington/DC/United States of America

The Lung Cancer Alliance HelpLine launched over 21 years ago and until recently was the only lung cancer-specific toll-free line in the United States. The reasons people call—for information, understanding, referral, compassion and most of all, hope—remain the same over time. But to keep pace with dramatic advances in the ways lung cancer is detected, diagnosed and treated, the LCA HelpLine has adapted quickly to meet the changing needs of our community. For many survivors and their loved ones, understanding lung cancer and its treatment is a challenge. Those impacted by the disease tend to be older, poorer and less educated, groups which also prefer to get their initial cancer information from their treatment teams. With competing time demands, treatment teams may not have enough time to ensure information is understood or be sensitive to providing it when the survivor can absorb, process and remember. Some are hesitant to admit they don’t understand all they have been told and are uncomfortable asking questions. Over the past 3.5 years, there have been nearly equal numbers of patients and caregivers calling the HelpLine. Roughly three-quarters of callers were women. In 2016, LCA began tracking more call statistics. Of those who told us the type of lung cancer, we see 83% NSLCC and 17% SCLC – quite representative of the lung cancer population. More than half (53%) were already in treatment. As the science has evolved and practice-changing discoveries are made, professional HelpLine staff provide up-to-date information, support and referrals to those in our community, no matter their place in the journey. The HelpLine provides the opportunity for in-depth conversations, problem solving and the development of questions to ask the team—it serves not as a substitute for conversations with treatment team but as support and complement to them. The LCA HelpLine also has grown with the internet. For some, the internet is a wealth of knowledge, psychosocial support and information. But sometimes even savvy users need help interpreting the information they have found. For others, the internet is a scary and overwhelming place, full of difficult statistics, conflicting recommendations and hard to understand concepts. Additionally, many in our community do not have access to the internet at all or lack broadband speeds that make it an effective tool. While the internet can be helpful, it does not take the place of contact with another caring person who can help. The HelpLine also gives us daily contact with lung cancer community and allows us to keep abreast of what lung cancer patients, their loved ones and those at risk need most. And as we listen, we adapt our services and programs to their needs. For example, we have recently started offering a new webinar series on the top symptoms and side effects reported by those in treatment and long-term survivors. Recently, the pace of scientific discovery and drug development in lung cancer has been accelerating rapidly. With six new drugs approved by the Food and Drug Administration in 2015 and countless new clinical trials launching to test not only new drugs but novel combinations of different classes of agents, patients and caregivers can be even more confused about the best treatment options for them. To address this changing environment, we have recently launched the LungMatch program to help patients find and understand personalized treatment options that they can discuss with their treatment team. LungMatch includes referrals to a concierge service for molecular testing if patients have not had it, a new, user-friendly online matching platform, and in-house personalized clinical trial navigation for interested callers on the HelpLine. The program is still in its infancy, but in the first month of tracking, we determined that 85% of callers asked had never been on clinical trials and only 50% reported molecular testing of the lung cancer. These early statistics indicate the widespread need in the lung cancer community. Through adapting to the changing needs of our community and helping them understand the evolving science, the HelpLine has been a lifeline for the lung cancer community in the United States for over 21 years.

**Keywords:** patient support, lung cancer, clinical trials, psychosocial support

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S115
SESSION YI01a: CLINICAL TRIALS & SCIENTIFIC MENTORING
SUNDAY, DECEMBER 04, 2016 - 08:00-09:45

YI01A.01 HOW TO IMPLEMENT AN IDEA/HYPOTHESIS INTO A CLINICAL TRIAL
Carlos Silva
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Last decades have shown an impressive advance in terms of biological knowledge in cancer. Traditional way to bring new ideas/hypothesis into clinical trials was overcoming by this fact. New agents directed against specific molecular targets have important impact in terms of response rate (RR), response duration (RD), progression free survival and eventually overall survival (OS) as well as quality of life (QoL). If you have an interesting idea/hypothesis, today you have to take on account several points that can exclude it. Select population becomes a very important issue. How to do this? Selecting a target, a tumor or both, or another conditions? Following the tradition of research phases, Phase I refers to measure safety and pharmacokinetics assessing maximum tolerated dose (MTD) but a number of new agents have a non reachable MTD because they have a low toxicity. On the other hand, phase II refers to the assessing of efficacy in a certain tumor as well as safety, but, in the case of new agents you may select a tumor (as usual), a specific target no matter what the tumor carry it (basket), or other conditions. In this phase measurement of response is important as a precedent of next phase trials and the challenge is the method you will use to do it. New immunotherapeutic agents probably need a different way to do this. Also, to have predictive biomarkers for most of these agents will be crucial to select the potential population that will achieve the more benefit and avoid futile toxicity and a waste of time and resources. We have to remember that biological effects not always means clinical benefit. Breaking barriers, for phase III comparator selection, primary and secondary end points as well as inclusion and exclusion criteria become a very important point and are different in the traditional way and in a proposed new way. OS is the gold standard end point but there are many more very important like PFS, RR, DoR, QoL. Again, measurement methods are very important and may be different related with biological mechanism and length of response for different agents than chemotherapy. As phase III trials select (include and exclude) patients throughout very strict criteria and there are some late toxicities that can be as important as the acute and subacute toxicities, phase IV trials are very important because they represent better the daily patient we see at office practice and is a powerful pharmacovigilance mechanism. Sanctorities have to be consider as far as the prevalent tumors have a very frequent involvement of Central Nervous System and these patient are mostly excluded from clinical trials at the begging. Ethics is a fundamental point as far as the most important objective is the patient safety and treatment accessibility. If we went troughout these restriction points and our idea/hypothesis has survive, we can follow the development of trials around waiting less time and resources.

Keywords: clinical trial, Targeted Therapies, idea/hypothesis, Response criteria

YI01A.02 BASIC STATISTICAL CONSIDERATIONS
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Introduction: Published and officially approved medical research is based on evidence and subsequently, statistical methods are an essential part in proving the usefulness of results. The translation in statistical terms in most cases is to build hypotheses and their alternatives to be tested. Clearly, medical researchers need some sound understanding of statistical principles which can be taken, however, not as a matter of course. The aim of the contribution is to communicate among readers of medical journals and reports statistical matters focusing on basic statistical considerations to enable a better understanding.

1 Essentials of statistical analysis and reporting: (i) Making the information content of the research results visible in summarizing and prescinding them in tables, graphs, and figures. (ii) Assessing and quantify any associations of reported measures like possible differences in the outcome of treatment actions etc., and using confidence intervals to express the uncertainty of those associations. (iii) Building hypotheses and their alternatives to prove that these associations have a real biological basis which is performed by statistical testing under a given level of significance (p-values). Important is the design of the research project: In randomized trials comparisons are an inherent part of those associations whereas in nonrandomized studies no direct conclusion can be driven that any association not due to chance indicates a causal relationship. Methods: Randomization is a process in which each of the patients has the same but not necessarily the equal chance to be assigned to predefined treatment arms ensuring that the treatment arms are comparable with respect to known or unknown risk factors. Hence, it is a method to remove selection and accidental bias and to guarantee the validity of statistical tests. Main design issues of studies are the formulation of the primary aim, the question of blinding, and the bound of consideration beyond a certain calculations. (2) Tables of baseline data and outcome events are part of most medical journal papers concerning treatments. Generally the first table displays the patients’ characteristics including some demographic variables and variables related to the primary aim. The main outcome events are forming the key table of every paper stratified by treatment groups. Categorical variables are shown as number and percent by group. Continuous variables can either be presented by mean and the standard deviation or by median and the interquartile range. Latter is preferred if the data are scattered and far from normal distribution with the implication that in the sequel non-parametric tests should be favored. For composite events like severe toxicities, progression of disease, and death the number of patients experiencing any of them plus the number in each component should be given, since we have the effect of multiple events. In focus are often variables displaying the time to the first event (e.g. progression of disease which can happen more than once during treatment history). For time events in the sequel interval of the general survival rate can be led to leading to special statistics and graphs. The Kaplan-Meier plot is the most used graph to show time-to-event outcomes as death, time to progression, disease free interval etc. In general the graph displays the steadily increasing difference in incidence rates of the outcome terms. To make this process clearer, the numbers at risk in each group should be shown at regular time intervals in the time axis. Individuals who did not reach the endpoint are censored (e.g. still alive, lost to follow-up) and should be marked in the plot. The conditional probabilities of Kaplan-Meier statistics indicate the probability of remaining the endpoint up to a certain time. This is important for making follow-up. Estimation of treatment effects is to measure the magnitude of the difference between treatments on patient outcomes. Normally this is done by a point estimate showing the actual difference observed. Inherent in this kind of statistics is that the bigger the trial, the more precise the point estimate will be. Such uncertainty is usually expressed by a 95% confidence interval in which this percentage of the sample will be found. The primary aim of the study determines the type of estimate required. Namely, there are three main types of outcomes: (a) Binary (dichotomous) response, e.g. dead or alive, progressive or non-progressive, success or failure, respectively. (b) Time to event outcome must be measured in intervals and can be evaluated by mean and the standard deviation or by median and the interquartile range. In randomized trials inclusion in the study to treatment failure. (c) Quantitative outcome as the reduction of a certain percentage of tumor loads at a given time point (e.g. a seen reduction of 30% after exactly 6 months). Estimates based in percentage are indicated if a binary outcome has to be judged in terms of absence or presence. Then a confidence interval should be given. Relative risks are the ratio of two percentages and can be converted to relative risk reduction. Alternatively relative odds can be applied which is a cross-product relationship and shows the relation of chance. Relative risk and relative odds are sometimes called risk ratio and odds ratio instead. The absolute difference in percentage is taken as a measure of absolute risk reduction. Estimates for time-to-event outcomes are used in all survival statistics as time to death, time to progression etc. The Kaplan-Meier plot depicts the first time of the occurrence of the event but does not in itself provide a simple estimate summarizing the treatment difference. The Kaplan-Meier estimate at the end of plotted time or at any other time between can be taken as cumulative rate of the leading event. That is only a time point estimate. Instead, the most common approach is to use a Cox proportional hazards model to obtain a hazard ratio and its 95% confidence interval. The hazard ratio can be thought of as the hazard rate in one group divided by the hazard rate in the other group averaged over the whole follow-up period. Examples from medical trials will be used to explain the statistical principles shown here.


Keywords: statistical principles, randomized clinical trials, interpretation of statistical terms, design of clinical trials

YI01A.04 CRITICAL EYE ON PRACTICE CHANGING LITERATURE
In Soo Lee
Center for Lung Cancer, National Cancer Center, Goyang-Si, Gyeonggi-Do/Korea, Republic of

Clinical trials in cancer have typically investigated agents or regimens...
in selected groups of patients based primarily on histology and clinical characteristics (e.g., tumor stage, performance status, prior treatment, etc.). The major goal of those trials was to demonstrate statistically significant improvement in outcome with a minimum p-value of 0.05, as compared with meaningful improvement in outcome. 

For lung cancer, it was recommended that one experimental agent in non-squamous NSCLC should be considered practice changing if it increases PFS by 4 months and OS by 3-4 months in a head-to-head comparison with the standard of care [3]. For NSCLC, it was recommended that one experimental agent in non-squamous NSCLC should be considered practice changing if it increases PFS by 3 months and OS by 3-4 months in a head-to-head comparison with the standard of care [3]. For NSCLC, it was recommended that one experimental agent in non-squamous NSCLC should be considered practice changing if it increases PFS by 3 months and OS by 3-4 months in a head-to-head comparison with the standard of care [3].

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Abstracts


**SESSION YI02: BASICS OF RADIO-ONCOLOGY**

**WEDNESDAY, DECEMBER 7, 2016 - 14:30-15:45**

**YI02.02 MODERN TREATMENT TECHNIQUES IN LUNG CANCER: THE ADVANTAGES OF CONFORMAL RADIOTHERAPY, IMRT AND PROTON THERAPY**

Satoshi Ishikura
Department of Radiology, Koshigaya Municipal Hospital, Koshigaya/Japan

As technology has advanced, modern radiotherapy (RT) techniques, such as conformal radiotherapy (CRT), intensity-modulated radiation therapy (IMRT), and proton therapy (PT), have become available. In this session, the advantages of these techniques in the treatment of early-stage and locally-advanced lung cancer will be discussed. Conformal RT uses CT scans to create 3-dimensional images of the tumor and normal tissues, which leads to more accurate treatment planning. It also uses multiple radiation beams from different angles to concentrate the radiation dose to the tumor while minimizing exposure to normal tissues. Conformal RT has been shown to improve tumor control and reduces toxicity compared to 2-dimensional RT (1). IMRT is a sophisticated form of CRT, which enables us to more exactly concentrate the dose to the tumor and spare normal tissues. It can also partially intensify doses to individual areas deemed to be more aggressive or more resistant to therapy. Spatially conformed with charged particles, IMRT provides a unique physical characteristic called the Bragg peak. The Bragg peak describes a certain tissue depth at which the protons stop just after transferring most of their energy. This feature is particularly convenient for tumors located close to critical normal tissues. PT is commonly adopted for pediatric, central nervous system, and intracranial or extracranial (such as brainstem, etc.) tumors. It is also called stereotactic ablative radiation therapy (SABR), is characterized by accurate target definition, precise tumor positioning, steep dose gradients outside targets, and very high dose per fraction. SBRT can be delivered using either CRT or IMRT. In the treatment of peripheral early-stage lung cancer, SBRT is widely adopted as a standard treatment and is considered better than conventional fractionated RT. PT can also be used in this setting, despite similar outcomes as SBRT (2); however, a recent systematic review of cost-effectiveness analyses did not support the use of PT (3). To improve outcomes in locally-advanced lung cancer, IMRT and PT have been actively investigated. Several in silico studies have suggested the superiority of IMRT over CRT, and PT over IMRT, but this remains to be demonstrated clinically. Subgroup analyses of RTOG 0617, which compared a high dose (74 Gy) vs. a standard dose (60 Gy) and allowed both CRT and IMRT, showed similar efficacy, less radiation pneumonitis, and better compliance of consolidative chemotherapy following IMRT over CRT, despite there being more advanced cases in the IMRT group (4). The study authors generated a hypothesis that dose intensification by IMRT may result in better efficacy with less toxicity. However, we could not determine the true difference between IMRT and CRT among patients who received the standard dose, which is our current practice, because their analysis included both high- and standard-dose arms; the differences might be more prominent in the high-dose arm. These investigators also suggested that increasing the radiation dose to the heart may worsen survival, so dose constraints to the heart became stricter thereafter. Results of a Bayesian phase II randomized trial of IMRT vs. PT were reported at the ASCO Annual Meeting earlier this year (5). The primary endpoint was incidence and time to protocol failure, defined as Grade 3 or higher pneumonitis or local failure. The observed local failure rates at 12 months were similar (13% vs. 12%). The investigators assumed Grade 3 or higher pneumonitis of 15% in the IMRT arm and 5% in the PT arm; however, they observed 6.5% in the IMRT arm, which was lower than the assumed probability, and 10.3% in the PT arm, higher than expected. Because this was a phase II trial with some limitations, firm conclusions could not be drawn. However, PT failed to suggest a clinical benefit over IMRT. A meta-analysis of the phase III trials conducted by the Radiation Therapy Oncology Group between 1988 and 2002 showed that new treatments were demonstrated to be better than existing ones in only 6 of 59 comparisons. In addition, overall survival of all the accrued patients did not differ between groups, while the odds ratio of 1.76 for treatment-related death was significantly higher for the new treatments (6). These results clearly showed that “New is not always better.” We need to identify the subpopulations for whom new techniques are more effective and to demonstrate these have true value with scientifically strong evidence, instead of just believing in their efficacy, complaining about the challenges associated with evaluating them, or advertising them directly to patients.

**Keywords:** mentor, mentee, career development, scientific mentoring

**References**


**Keywords:** lung cancer, Proton therapy, Conformal Radiotherapy, Intensity Modulated Radiation Therapy

**YI02.03 DOSE LIMITATIONS FOR RADIOTHERAPY OF LUNG CANCER**

Antonio Juretic1, Ana Frobe1, Jasmina Maric Brozic2, Lea Galunic Bilic3

**SESSION YI02: BASICS OF RADIO-ONCOLOGY**

**WEDNESDAY, DECEMBER 7, 2016 - 14:30-15:45**
Radiotherapy treatment intent depends on tumor extent (disease stage), tumor location, patient’s performance status and comorbidities, availability of modern radiotherapy treatment machines and their technical and software capabilities (14). Radiotherapy with curative intent is indicated as an alternative to surgical treatment in patients having the early stage disease (generally stages I and II) or a locally more advanced disease (stage III). In early stage cases, decisions which are the group for radiotherapy or surgery can be applied as, for example, the sole treatment modality in the form of hypofractionated stereotactic ablative radiotherapy (SABR) for patients with lymph node-negative peripheral non-small cell lung cancer (NSCLC). For patients having inoperable locally advanced lung cancer (stage III) the five-year overall survival rate is around 15-20%. Therefore, the two remaining standard treatment modalities, chemotherapy and radiotherapy with curative intent, are used and combined whenever possible. Comitant chemoradiotherapy is the treatment of choice since it gives better results, but in practice a significant number of patients is not fit for this approach. Therefore, the alternative in usual patients is conventional radiotherapy. Conventional radiotherapy is the therapy of choice for patients having concomitant chemoradiotherapy there are no results in favor of induction or consolidation chemotherapy. It might be that a novel targeted immunotherapy approach with anti-PD-1 or anti-PD-L1 inhibition will in the future improve the survival rate of this group of patients and patients with the most advanced cases. The effective and safe dose delivery for the total radiotherapy dose being allocated is generally based for most tumors there is a dose-response effect, i.e., the higher the dose, the higher the chance of local tumor control and cure. The first trial that in the case of lung cancer demonstrated this was the RT01 trial (5). In this dose escalation trial, the dose of 60 Gy in comparison with the dose of 50 and 40 Gy was found, clinically, to have a lower incidence of local failures (33% versus 39% versus 44% to 49%). The survival of patients according to treatment regimen was not statistically significantly different. The one-year and two-year survival rates for all groups were, respectively, 65% and 59%. On the basis of this trial the dose of 60 Gy in 30 fractions (60 Gy/30x) or higher has since that time been the optimal standard radiotherapy treatment, although patient outcomes were objectively very poor. It should be mentioned that from today’s perspective the radiotherapy techniques that were then used (2D radiotherapy or 3D conformal radiotherapy) and relatively large treatment volumes are not recommended nowadays in radiotherapy treatments with curative intent (3.4). The objectively unsatisfactory clinical outcomes in terms of local tumor control, progression free survival (PFS) and overall survival (OS) after radiotherapy +/- chemotherapy treatments are probably the consequence of the inadequate treatment dose to the tumor targets. However, the usual radiotherapy doses is limited by the radiation tolerance of surrounding normal tissues and organs (3.4). In clinical radiotherapy, the radiation tolerance of normal tissues and organs surrounding the tumor limits the radiotherapy dose that can be given safely. As the dose is increased, the incidence and severity of normal tissue damage increases. When severe, normal tissue damage can promote the threatening morbidities. Multiple parameters such as total radiotherapy dose, fraction size, overall treatment time, volume and type of normal tissues to be irradiated, definition of target volume, and quality control of radiotherapy techniques should be taken into account. A reduction of radiotherapy-related toxicity is fundamental to the improvement of clinical results in every cancer as well as other types of cancers. Organs at risk of lung cancer radiotherapy include the lungs, heart, spinal cord, and esophagus. Present knowledge of radiation toxicity is derived from conventional and newer 3D conformal radiotherapy (3D-CRT) data. The QUANTEC project (6) produced data that are currently used to predict the side effects of radiotherapy and the plausibility of evaluated treatment plans. Before being approved all radiotherapy treatment plans have to be evaluated for the probability of organ-specific radiation toxicity (3.4). Thanks to the evolving radiation imaging and computer technology, a number of new innovations and techniques have been developed in radiotherapy treatment in the several past decades. Conventional 2D radiotherapy treatment simulation has been replaced with computer tomography (CT) planning, with volumes delineated according to the International Commission on Radiation Units and Measurements (ICRU) report and ICRU supplements. This CT-based planning technique with modern computer software and image analysis techniques such as PET/CT and MRI have enabled more precise target borders and volume delineation with the consequence of radiotherapy treatment plans having better tumor dose conformity and sparing the surrounding normal tissues (3.4). Due to a better delineation of tumor margins and reduced rates of radiation-associated toxicity, the current standard radiation treatments based on the implementation of these various technical and technological advances in radiation planning and delivery have allowed the design of clinical studies with radiotherapy dose escalations and modified fractionation schemes. The goal of radiation treatment is to improve clinical outcomes while reducing the damage to the normal tissues. Newer radiotherapy equipment, techniques and treatment planning software can, due to a better delineation of tumor margins and reduced rates of radiation-associated toxicity, allow tumor dose escalation to this relationship was publishable tumor cure. Improvements in radiotherapy technique are achieved by using functional images for target definition (PET/CT), 4D-computed tomography (4D-CT), intensity modulated radiation therapy (IMRT) and adaptive radiotherapy. (3.4) Several studies have shown a better response with dose escalation in NSCLC. Doses of up to 74 Gy can be delivered without normal tissue constraint being crossed. The RTOG 0617 trial has reported the outcome of a dose-escalated 3D conformal radiotherapy in stage I-III NSCLCs stratified at escalation dose level according to parameters V20 Gy (percentage of the total lung volume that received ≥20 Gy). The results of this trial showed that radiation dose escalation was considered safe when using 3D conformal radiation treatment planning, with volumes irradiated to V20 Gy ≤25% in patients with V20 between 25 and 36% (7). In the RT0617 trial two schedules were compared: 60 Gy (in 6 weeks) versus 74 Gy (in 7.5 weeks) in a 2+2 design where patients were also randomized to receive or not receive cetuximab. Surprisingly, the higher dose arm was not associated with improved survival at 1 year, rather, showed potential of reduced treatment toxicity. The trial showed OS of 28.7 months for patients who received standard dose radiotherapy compared with 20.3 months for those who received high dose radiotherapy. Median survival in patients who received cetuximab was 21.3 months compared to 24.0 months in those who did not receive cetuximab (p = 0.05). The use of IMRT allows dose escalation to lung V5, V10 and V20% with reduced volumes of target volume and may improve survival. However, several technical factors, such as dose escalation, are required to ensure adequate and safe delivery.
TKI. The impact of plasma L858R levels at disease progression on subsequent study. Different changing types were correlated with benefits from EGFR-mutation during EGFR-TKI treatment based on a prospective randomized P (95%CI, 16.5–22.9) and 16.0 months (95%CI, 13.4–18.5), respectively (PFS was 11.1 (95%CI, 6.6–15.6) and 7.5 months (95%CI, 1.4–13.6) in patients L858R maintained a stable level when disease progressed (Stable Type). Median the time of best response to EGFR-TKI. In 61 patients, L858R increased to its quantitative polymerase chain reaction. Changing types of plasma L858R erlotinib or gefitinib. Serial plasma L858R in 80 patients was detected using blood samples as pre-planned scheduled. Patients were randomized to receive Totally, 256 patients were enrolled in CTONG0901. One hundred and eight tumor (CTONG0901). Serial plasma samples were collected as a pre-planned schedule. Several studies have reported a correlation rate between tumor and plasma - 90%, even reaching 97%, demonstrating the feasibility of detecting EGFR mutations in ctDNA. EGFR mutation status detection in ctDNA has been approved by the European Society for Medical Oncology and by China to be used with EGFR-TKI treatment for NSCLC. In addition to providing pretreatment information, plasma-based EGFR mutation detection makes it possible to monitor dynamic changes in this mutation during treatment. Several studies have reported a quantitative change in EGFR mutations during EGFR-TKI treatment by comparing pre- and post-treatment plasma, in which various types of plasma EGFR mutations were found. The quantity of the plasma EGFR mutation sometimes decreases, or sometimes decreases slowly or rapidly. Patients whose plasma EGFR mutations decrease rapidly usually exhibit a better response to EGFR-TKI treatment. However, these studies were not based on prospective clinical trials, therefore the number of patients who had serial plasma specimens tested during EGFR-TKI treatments was limited, and very few plasma specimens were collected as part of a pre-planned schedule. The only recent study on plasma EGFR mutation changes based on a prospective clinical trial was reported by Mok et al. In this phase III trial (FASTACT-2), patients received gemicatbine/platinum plus sequential erlotinib or placebo. EGFR mutation-specific ctDNA levels decreased at cycle 3 and increased at the time of disease progression. Positive plasma EGFR mutant DNA at cycle 3 predicted a worse clinical outcome. In this study, the treatment was chemotherapy plus EGFR-TKI or placebo, not EGFR-TKI, and there was no information on the plasma EGFR mutation at other time points except at baseline, cycle 3, and at disease progression. The dynamic changing types of plasma EGFR mutations during the whole course of EGFR-TKI treatment were not distinguished from clinical outcomes, and therefore does not accurately represent the true proportion of patients who responded to EGFR-TKI mutations. To measure changes of plasma EGFR L858R mutation during EGFR-TKI treatment, and to determine its correlation with the response and resistance to EGFR- TKI, we conducted a study. This study was a pre-planned exploratory analysis of a randomized phase III trial conducted from 2009 to 2014 comparing erlotinib with gefitinib in advanced NSCLC harboring EGFR mutations in tumor (CTONG0901). Serial plasma samples were collected as a pre-planned schedule. This trial was conducted in Guangdong Lung Cancer Institute, China. Totally, 256 patients were enrolled in CTONG0901. One hundred and eight patients harbored L858R mutation in tumors and 80 patients provided serial blood samples as pre-planned scheduled. Patients were randomized to receive erlotinib or gefitinib. Serial plasma L858R in 80 patients was detected using quantitative polymerase chain reaction. Changing types of plasma L858R were analyzed using Ward's Hierarchical Clustering Method. Progression-free survival (PFS) and overall survival (OS) were compared between different types. As a whole, the quantity of L858R decreased and reached the lowest level at the time of best response to EGFR-TKI. In 61 patients, L858R increased to its highest level when disease progressed (Ascend Type), while in 19 patients, L858R maintained a stable level when disease progressed (Stable Type). Median PFS was 11.0 (95%CI, 6.6–15.6) and 75.9 months (95%CI, 1.1–4.3) in patients with Ascend and Stable Types, respectively (P = 0.23). Median OS was 19.7 (95%CI, 16.5–22.9) and 16.0 months (95%CI, 13.4–18.5), respectively (P = 0.050). This is the first report finding two different changing types of plasma L858R mutation during EGFR-TKI treatment based on a prospective randomized study. Different changing types were correlated with benefits from EGFR- TKI. The impact of plasma L858R levels at disease progression on subsequent treatment strategy needs further exploration. This study was recently published in Journal of Hematology&Oncology. In summary, liquid biopsy is very promising in monitoring dynamic changes of driver genes in advanced NSCLC, which promotes the development of precision medicine. References 1. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N. Engl. J. Med. 2009;361(10):947-957. 2. Kimura H, Suminoe M, Kasahara K, et al. Evaluation of epidermal growth factor receptor mutation status in serum DNA as a predictor of response to gefitinib (IRESSA). Br. J. Cancer. 2007;97(6):778-784. 3. Douillard JY, Ostoros G, Cobo M, et al. 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CIRCULATING TUMOR DNA BY DIGITAL NGS IN PATIENTS WITH LUNG CANCER
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Background: Next generation sequencing (NGS) has been increasingly used in oncology practice but proven practically difficult when serial tumor samples are needed. The objectives of this study were to determine feasibility and explore clinical utility of serial NGS analyses of circulating tumor DNA (ctDNA) in patients (pts) with advanced solid tumors undergoing treatment. Methods: ctDNA digital NGS was performed by a CLIA-certified lab (70-gene panel with mutant allele fraction (MAF) quantification). ctDNA results were retrospectively analyzed and decreases/increases/stability of molecular tumor load (MTL) defined as MAFs of trunclal driver mutations correlated with clinical and radiographic response to treatment (response, progression, or stable disease, respectively). Results: From Jan 2015 to July 2016, 38 consecutive pts with advanced lung tumors (84% LUAD, 5% LUSC, 5% SCLC, 5% NOS) receiving treatment (Table) had serial ctDNA analyses (median 2, range 2-7). ctDNA alterations were detected at least once in 37 (97.4%) pts. Changes in MTL correlated with or predicted all (95% CI, 82.0-99.8%) radiological and/or clinical responses except for the patient with no genomic alteration detected. MTL results clarified response status when radiographic responses were difficult to assess in 9 (28%) of pts with either complex pleural disease (n=6), pneumonitis due to PD-1 inhibitor therapy (2). Two MTL change patterns were observed: 1) clonal changes while receiving targeted therapy, including EGFR (12), ALK (3), MET (2), EBRB2 (2); 2) global changes to PD-1 inhibitors, chemotherapy or radiation. Representative tumor response maps will be presented.

Table: Summary of tumor types and cancer treatment.

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Targeted Therapy</th>
<th>Immuno-therapy</th>
<th>Chemo-therapy</th>
<th>Radiation</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>LUAD</td>
<td>14</td>
<td>8</td>
<td>1</td>
<td>3</td>
<td>32</td>
</tr>
<tr>
<td>LUSC</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>SCLC</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>NOS</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>All</td>
<td>16</td>
<td>9</td>
<td>10</td>
<td>3</td>
<td>38</td>
</tr>
</tbody>
</table>

Conclusion: Serial liquid biopsies and ctDNA digital NGS are feasible and clinically useful in monitoring MTL and genomic alterations during cancer treatment, especially in situations when radiographic responses are equivocal. Prospective evaluation of impact on clinical decision making is warranted.

JCES01: JOINT IASLC - CHINESE SOCIETY FOR CLINICAL ONCOLOGY - CHINESE ALLIANCE AGAINST LUNG CANCER SESSION SUNDAY, DECEMBER 04, 2016: 08:00-11:45

JCES01.14 MUTATIONAL PROFILING OF NON-SMALL-CELL LUNG CANCER PATIENTS RESISTANT TO FIRST-GENERATION EGFR TYROSINE KINASE INHIBITORS USING NEXT GENERATION SEQUENCING
Ying Jin1, Xinmin Yu2, Xin Shi3, Yipeng Zhang1, Guangyuan Lou2
1Zhejiang Cancer Hospital, Hangzhou, China; 2Medical Oncology, Zhejiang Cancer Hospital, Hangzhou/China

Background: Patients with advanced non-small-cell lung cancer (NSCLC) harboring sensitive epithelial growth factor receptor (EGFR) mutations invariably develop acquired resistance to EGFR TKIs. Although previous research have identified several mechanisms of resistance, the systematic evaluation using next generation sequencing (NGS) to establish the genomic mutation profiles at the time of acquired resistance has not been conducted. Methods: In our single center, we performed NGS of EGFR gene-defined set of 46 cancer-related genes in a cohort of 97 patients with NSCLC harboring TKI-sensitive EGFR mutations at the time of acquired resistance to first-generation EGFR-TKIs between January 2015 to December 2015. Results: In 97 samples we found total 345 gene alterations (mean 3.6 mutations per patient, range 1-10). Fifty-six patients (57.7%) still exhibit EGFR-sensitive mutations as pretreatment, 93 patients (95.9%) exhibit at least one mutation except for previous existed EGFR-sensitive mutations. In all the 97 patients, most frequently mutated genes were TP53 (39.8%), 7900M (28.9%), TE2 (11.3%), EGFR amplification (10.3%), PIK3CA (8.2%), BIM (6.2%), KRAS (7.2%), APC (7.2%), RBL1 (6.2%), HER2 (6.2%), DNMT3A (6.2%) and MET (5.2%). Conclusion: NGS in this study uncovered many new genetic alterations potentially associated with EGFR TKI resistance and provided information for the further study of drug resistance and corresponding relevant tactics against the challenge of disease progression.

JCES01.15 ANALYSIS OF GENOMIC ALTERATIONS AND HETEROGENEITY IN PULMONARY ADENOID CYSTIC CARCINOMA BY NEXT-GENERATION SEQUENCING
Min Li, Bingrong Zhao, Pengbo Deng, Liming Cao, Huaping Yang, Qihua Gu, Chengping Hu
Department of Respiratory Medicine, Xiangya Hospital, Central South University, Changsha/China

Background: Pulmonary adenoid cystic carcinoma (PACC) is one of the rare malignancies, that primary from glandular tissues of lung. Currently, the treatment of PACC relies on surgery and local radiotherapy. However the therapy for advanced PACC patients is limited. A large number of studies demonstrated that advanced PACC patients obtained little benefit from chemotherapy. Moreover, only a few case reports revealed PACC patients were appropriate for target therapy. Using high-flux and high-resolution techniques to detect the genomic alterations of PACC could provide theoretical foundation for the precision therapy of PACC. Methods: 8 PACC patients who received surgical resection between January 2013 to December 2015 were enrolled. The tumor tissues from different locations and blood samples were collected. The oncoscreen10 panel by illumina platform, which utilizing probe hybridization to gathering 287 exom regions and 22 intron regions, were used to detect the genomic alteration status of PACC. And the blood system mutations were filtered by contrasting the gene mutation status of the leukocytes. The tumor heterogeneity was revealed by comparing the gene mutation status in different areas of the same PACC, and the phylogenetic relationships were analyzed to disclose the evolving and developing progression of PACC. Results: There were 69 gene mutations together among 8 patients including 29 samples. Each patient has 8.6 mutations averagely.

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The high-frequency mutations were PAK3-D219E, FBXW7-D112E, TET2-T418I, KAT6A-E796A, and MET-R1005Q. However, the common mutations in other NSCLC, like EGFR, KRAS, ALK, etc., weren't happened in this group of PACC. In this study, the spatial heterogeneity was discovered in PACC, not only in the mutation site, but also in the mutant abundance. Moreover, the phylogenetic relationships revealed that the clonal evolution and development existed in PACC. Conclusion: The status of genomic alterations in PACC was different from the other non-small cell lung cancer (NSCLC). PACC showed obvious spatial heterogeneity and clonal evolution.

JCES01: JOINT IASLC: CHINESE SOCIETY FOR CLINICAL ONCOLOGY: CHINESE ALLIANCE AGAINST LUNG CANCER SESSION
SUNDAY, DECEMBER 04, 2016: 08:00-11:45

JCES01.16 A MET INHIBITOR IN THE TREATMENT OF METASTATIC NON SMALL CELL LUNG CANCER WITH MET AMPLIFICATION
Tongtong Zhang1, Junling Li2
1Department of Medical Oncology, Cancer Institute & Hospital, Peking Union Medical College/Chinese Academy of Medical Science, Beijing, China; 2Cancer Institute & Hospital, Peking Union Medical College/Chinese Academy of Medical Science, Beijing, China

Background: Amplification of the mesenchymal-epithelial transition factor (MET) gene plays a vital role in non-small cell lung cancer (NSCLC). The anti-MET therapeutic strategies are still unclear in epidermal growth factor receptor (EGFR) mutant patients and EGFR-naive patients. Aim of our study is to discuss role of MET amplification in NSCLC patients, and evaluate the anti tumor activity of crizotinib (MET inhibitor) in Chinese NSCLC patients with MET gene amplification. Methods: From Jun 2015 to Jan 2016, we detected 11 metastatic NSCLC patients with MET amplification by fluorescence in situ hybridization (FISH). MET amplification was defined as gene focal amplification or high polyomorphy (at least 15% cells ≥5 copy numbers). Patients with MET de novo amplification received crizotinib, patients with concomitant MET acquired amplification and EGFR mutation received combined therapy of EGFR-tyrosine kinase inhibitors (TKIs) (gefitinib, erlotinib, icotinib) and crizotinib. All enrolled subjects received tumor measurement according to RECIST1.1 Results: The frequency of MET de novo amplification was 54.5% (6/11), and that of concomitant MET acquired amplification and EGFR mutation was 45.5% (5/11). Respectively, 4 of 6 patients with MET de novo amplification received crizotinib, 2 patients had partial response (PR), 1 patient had stable disease (SD), 1 patient died due to heart disease. Response rate (RR) of crizotinib was 50% (2/4). Encouraging response was observed in one case, a CT scan performed 31 days after starting crizotinib revealed 42.2% decrease in tumor measurement, until now, a 7-month CT revealed 60.0% decrease. 3 of 5 patients with concomitant MET acquired amplification and EGFR mutation received the combined therapy of EGFR-TKIs and crizotinib. 1 patient achieved PR, 2 patients had SD. RR of combined therapy was 33.3% (3/9). Dramatic response was observed in one case with combined therapy, a 2-month CT revealed 31.0% decrease in metastatic burden. Conclusion: According to our study, patients with MET acquired amplification and EGFR mutation need combined therapy.

JCES01: JOINT IASLC: CHINESE SOCIETY FOR CLINICAL ONCOLOGY: CHINESE ALLIANCE AGAINST LUNG CANCER SESSION
SUNDAY, DECEMBER 04, 2016: 08:00-11:45

JCES01.17 A PHASE I DOSE EXPANSION STUDY OF EPITINIB TO EVALUATE EFICACY AND SAFETY IN NSCLC PATIENTS WITH BRAIN METASTASIS
Qing Zhou1, Bin Gan2, Qunying Hong1, Mengzhao Wang1, Xiaoqiong Liu1, Liwei Yuan1, Ye Hua1, Hongcan Ren1, Weiguo Su1, Yi Long Wu2
1Guangdong Lung Cancer Institute, Guangdong General Hospital & Guangdong Academy of Medical Sciences, Guangzhou, China; 2Department of Medical Oncology, Cancer Institute & Hospital, Peking Union Medical College, Chinese Academy of Medical Sciences, Beijing, China

Background: A significant portion of patients with non-small cell lung cancer (NSCLC) develop brain metastasis. Patients with brain metastasis suffer from poor prognosis with a median survival of less than 6 months and low quality of life with limited treatment options. First generation EGFR tyrosine kinase inhibitors (EGFR TKIs) have demonstrated significant clinical benefit for patients with EGFR-mutant NSCLC. However, their effect on brain metastasis is limited due to poor drug penetration into the brain. Epitinib is an EGFR TKI designed to improve brain penetration. A Phase I dose escalation study on epitinib has been completed and the recommended Phase 2 dose (RP2D) determined (Y-L Wu, 2016 ASCO). This Phase I dose expansion study was designed to evaluate the efficacy and safety of epitinib in EGFR-mutant NSCLC patients with brain metastasis. Methods: This is an ongoing open label, multi-center Phase I dose expansion study. EGFR-mutant NSCLC patients with confirmed brain metastasis, either prior EGFR TKI treated or EGFR TKI treatment naïve, were enrolled to receive oral epitinib 160 mg per day. Patients with extra-cranial disease progression while on treatment with an EGFR TKI were excluded. Tumor response was assessed per RECIST 1.1. Results: As of 31 May, 2016, 27 patients (13 EGFR TKI pretreated, 14 EGFR TKI treatment naïve) have been enrolled and treated with epitinib. The most frequent adverse events (AEs) were skin rash (89%), elevated ALT (4%)/AST (37%), hyper-pigmentation (4%) and diarrhea (30%). The most frequent Grade 3/4 AEs were elevations in ALT (19%), gamma-GGT (11%), AST (7%), hyperbilirubinemia (7%) and skin rash (4%). There have been no Grade 5 AEs to date. Among the 24 evaluable patients (11 TKI pretreated, 13 TKI naïve), 7 (7/24, 29%) achieved a partial response (PR), including 1 unconfirmed PR. All PRs occurred in EGFR TKI treatment naïve patients (7/13, 53.8%). Of the 24 evaluable patients, 8 (5 EGFR TKI treatment naïve, 3 EGFR TKI pretreated) had measurable brain metastasis (lesion diameter >10 mm per RECIST 1.1) with 2 PRs (both EGFR TKI treatment naïve patients, 2/5, 40%). Conclusion: Epitinib 160mg per day treatment in EGFR-mutant NSCLC patients with brain metastasis demonstrated clinical activity both extra- and intra-cranial. Epitinib was well tolerated. The data to date appears encouraging and warrants further development of epitinib.

JCES01.18 DUAL POSITIVE PD-L1 AND CD8+ TIL REPRESENTS A PREDOMINANT SUBTYPE IN NSCLC AND CORRELATES WITH AUGMENTED IMMUNOGENICITY
Si-Yang Liu1, Zhong-Yi Dong2, Wen-Zhao Zhong3, Si-Pei Wu4, Zhi-Xie5, Hai-Yan Li6, Yi Long Wu2
1Guangdong Lung Cancer Institute, Guangdong General Hospital & Guangdong Academy of Medical Sciences, Guangzhou, China; 2Guangdong Lung Cancer Institute, Guangdong General Hospital, Guangzhou, China; 3Department of Pulmonary Oncology, Guangdong General Hospital & Guangdong Academy of Medical Sciences, Guangzhou, China; 4Guangdong Lung Cancer Institute, Guangdong General Hospital & Guangdong Academy of Medical Sciences, Guangzhou, China; 5Guangdong Cancer Institute, Guangdong General Hospital & Guangdong Academy of Medical Sciences, Guangzhou, China

Background: Recent studies have identified that the degree of tumor infiltrating lymphocyte (TIL) infiltration and PD-L1 expression in the tumor microenvironment (TME) are significantly correlated with the clinical outcomes of anti-PD-1/PD-L1 therapies. Here we conducted this study to verify the distribution of PD-L1/CDB TIL expression and its clinical significance in non-small cell carcinoma (NSCLC). Potential mechanism predicted for PD-1 blockade was explored in depth as well. Methods: Immunohistochemistry was performed to detect PD-L1 and CD8 expression in NSCLC. The Kaplan–Meier (KM) survival curve was used to estimate disease free survival (DFS) and overall survival (OS). Gene Set Enrichment Analysis (GSEA) was used to determine potentially relevant gene expression signatures. Results: 288 cases with stage I–IIIA NSCLC were evaluated for PD-L1 and CD8+ TIL staining. Dual positive PD-L1 and CD8+ TIL staining, Dual positive PD-L1 and CD8+ TIL staining, Dual positive PD-L1 and CD8+ TIL staining, Dual positive PD-L1 and CD8+ TIL staining, Dual positive PD-L1 and CD8+ TIL staining, Dual positive PD-L1 and CD8+ TIL staining, Dual positive PD-L1 and CD8+ TIL staining, Dual positive PD-L1 and CD8+ TIL staining, Dual positive PD-L1 and CD8+ TIL staining. Conclusion: Dual positive PD-L1 and CD8+ TIL staining, Dual positive PD-L1 and CD8+ TIL staining, Dual positive PD-L1 and CD8+ TIL staining, Dual positive PD-L1 and CD8+ TIL staining, Dual positive PD-L1 and CD8+ TIL staining, Dual positive PD-L1 and CD8+ TIL staining, Dual positive PD-L1 and CD8+ TIL staining, Dual positive PD-L1 and CD8+ TIL staining, Dual positive PD-L1 and CD8+ TIL staining. The status of genomic alterations in PACC was different from the other subgroups. Furthermore, we analyzed the correlation between expression types of PDL1/CDB and mutation burden and antigen presentation. We identified dual positive PD-L1 and CD8 was significant with increased mutation burden (p<0.001), high frequency of mismatch repair (MMR) related gene mutation. More interestingly, tumor with dual positive PD-L1 and CD8 manifested a remarkable activated antigen presentation and T cell receptor signature compared with other subgroups. Conclusion: Dual positive PD-L1 and CD8 was identified as a predominant subtype in NSCLC and correlates with increased immunogenicity. These findings provide the evidence that combined analysis of PD-L1 and CD8 in NSCLC may be promising way to predict PD-1 blockade immunotherapy.

JCES01.19 CLINICOPATHOLOGIC CHARACTERISTICS,
GENETIC VARIABILITY AND THERAPEUTIC OPTIONS OF RET Rearrangement Patients in Lung Adenocarcinoma

Zhengbo Song1, Ximin Yu2, Yingping Zhang3
1Medical Oncology, Zhejiang Cancer Hospital, Hangzhou/China; 2Zhejiang Cancer Hospital, Hangzhou/China

Background: RET fusion gene is identified as a novel oncogene in a subset of non-small cell lung cancer (NSCLC). However, few data are available about the prevalence, clinicopathologic characteristics, genetic variability and therapeutic options in RET-positive lung adenocarcinoma. We determined the expression of thymidylate synthetase (TS) to provide a rationale for the efficacy results. Methods: For 615 patients with lung adenocarcinoma, RET status was detected by reverse transcription-polymerase chain reaction (RT-PCR). Next-generation sequencing (NGS) and FISH were performed in positive cases. Thymidylate synthetase (TS) mRNA level was assayed by RT-PCR. Overall survival (OS) was evaluated by Kaplan-Meier method and compared with log-rank test. Results: Twelve RET-positive patients were identified by RT-PCR. However, one patient failed the detection of RET arrangement by FISH and NGS. Totally, 11 patients (1.8%) confirmed with RET rearrangements by three methods, including six females and five males with a median age of 54 years. The presence of RET rearrangement was associated with lepidic predominant lung adenocarcinoma subtype in five of 11 patients. RET rearrangements comprised of nine KIF5B–RET and two CDDC6–RET fusions. Four patients had concurrent gene variability by NGS detection, including EGFR(n=1), MAP2K1(n=1), CTNNB1(n=1) and AKT1(n=1). No survival difference existed between RET-positive and negative patients (58.1 vs. 52.0 months, P=0.504). The median progression-free survival of first-line pemetrexed/platinum regimen was 7.5 months for four recurrent cases, and longer than RET-negative patients (7.5 vs. 5.0 months, P=0.026). The level of TS mRNA was lower in RET-positive patients than that in those RET-negative counterparts (292±18×10–4 vs. 394±45×10–4, P=0.019). Conclusion: The prevalence of RET fusion is approximately 1.8% in Chinese patients with lung adenocarcinoma. RET arrangement is characterized by lepidic predominance and a lower TS level. RET-rearranged patients may benefit more from pemetrexed-based regimen.

PULMONARY NEUROENDOCRINE CARCINOMA WITH COMPLETELY RESECTION

Guangyuan Lou1, Zhengbo Song2, Yingping Zhang3
1Zhejiang Cancer Hospital, Hangzhou/China; 2Medical Oncology, Zhejiang Cancer Hospital, Hangzhou/China

Background: According to the 2015 World Health Organization classification of lung tumors, pulmonary large cell neuroendocrine carcinoma (PLCNC) is grouped with the small cell lung cancer (SCLC) and carcinoid as pulmonary neuroendocrine carcinoma (PNC) for the common features of neuroendocrine characteristics. Molecular profiles and classification of primary pulmonary neuroendocrine carcinoma(PNC) are not well investigated currently. We conducted present study to evaluate genomic abnormality and survival in patients with primary PNC. Methods: Tumor samples of PNC after completely resection from Zhejiang Cancer Hospital were collected from 2008 to 2015. Nine driver genes including six mutation (EGFR, KRAS, NRAS, PIK3CA, BRAF, HER2) and three fusions (ALK, ROS1, RET) were evaluated by RT-PCR. Survival analysis was evaluated using the Kaplan-Meier method. Results: Totally, 108 patients with pathologic confirmed PNC were enrolled. Samples included 52 PLCNC, 44 small cell lung cancer (SCLC) and 12 carcinoid. Twelve patients were found to harbor genomic aberrations (11.1%). The most frequent gene abnormality was PIK3CA (n=5,5.6%), followed with EGFR (n=3,3.2%), KRAS (n=2,1.9%), ALK (n=1,0.9%), RET (n=1,0.9%). No ROS1, BRAF, NRAS and HER2 mutations were observed. The frequencies of gene aberrations in PLCNC, SCLC and carcinoid were 15.4, 6.8% and 8.3%, respectively. Sixty-seven patients were patients with recurrence or metastasis after surgery, including 32 PLCNC, 33 of SCLC, and two of carcinoid (both were atypical carcinoid). Among the 32 patients with PLCNC, none received molecular targeted treatment, 28 received first-line chemotherapy, including 18 of etoposide/platinum regimen and 10 of other platinum-based treatment. The progression free survival in patients with etoposide/platinum regimen was longer than patients with non-etoposide/platinum treatment (4.8 vs. 3.4 months, P=0.019). Survival difference was observed among the PLCNC, SCLC and carcinoid group (37.0 vs. 34.0 vs not reached, P=0.035), but no difference existed between the PLCNC and SCLC group (P=0.600). Conclusion: Common genomic abnormality is rare in PNC patients and most frequently observed in PLCNC. Patients with carcinoid had a superior survival than PLCNC and SCLC.

PULMONARY NEUROENDOCRINE CARCINOMA WITH COMPLETELY RESECTION

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Background: According to the 2015 World Health Organization classification of lung tumors, pulmonary large cell neuroendocrine carcinoma (PLCNC) is grouped with the small cell lung cancer (SCLC) and carcinoid as pulmonary neuroendocrine carcinoma (PNC) for the common features of neuroendocrine characteristics. Molecular profiles and classification of primary pulmonary neuroendocrine carcinoma(PNC) are not well investigated currently. We conducted present study to evaluate genomic abnormality and survival in patients with primary PNC. Methods: Tumor samples of PNC after completely resection from Zhejiang Cancer Hospital were collected from 2008 to 2015. Nine driver genes including six mutation (EGFR, KRAS, NRAS, PIK3CA, BRAF, HER2) and three fusions (ALK, ROS1, RET) were evaluated by RT-PCR. Survival analysis was evaluated using the Kaplan-Meier method. Results: Totally, 108 patients with pathologic confirmed PNC were enrolled. Samples included 52 PLCNC, 44 small cell lung cancer (SCLC) and 12 carcinoid. Twelve patients were found to harbor genomic aberrations (11.1%). The most frequent gene abnormality was PIK3CA (n=5,5.6%), followed with EGFR (n=3,3.2%), KRAS (n=2,1.9%), ALK (n=1,0.9%), RET (n=1,0.9%). No ROS1, BRAF, NRAS and HER2 mutations were observed. The frequencies of gene aberrations in PLCNC, SCLC and carcinoid were 15.4, 6.8% and 8.3%, respectively. Sixty-seven patients were patients with recurrence or metastasis after surgery, including 32 PLCNC, 33 of SCLC, and two of carcinoid (both were atypical carcinoid). Among the 32 patients with PLCNC, none received molecular targeted treatment, 28 received first-line chemotherapy, including 18 of etoposide/platinum regimen and 10 of other platinum-based treatment. The progression free survival in patients with etoposide/platinum regimen was longer than patients with non-etoposide/platinum treatment (4.8 vs. 3.4 months, P=0.019). Survival difference was observed among the PLCNC, SCLC and carcinoid group (37.0 vs. 34.0 vs not reached, P=0.035), but no difference existed between the PLCNC and SCLC group (P=0.600). Conclusion: Common genomic abnormality is rare in PNC patients and most frequently observed in PLCNC. Patients with carcinoid had a superior survival than PLCNC and SCLC.
negative. AXd, cobas, ddPCR, and firefly NGS uncovered 73, 69, 70, and 68 EGFR wild-type loci, respectively. The concordance and negative coincidence rates between any two platforms were over 90%. Conclusion: The detection rate and concordance were probably affected by the abundance of EGFR mutations and the sensitivity of different platforms. Three platforms, including cobas, ddPCR, and firefly NGS, exhibited higher positive coincidence and detection rates when the allele frequency was lower than 1%.

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JCES01:23 EGFR MUTATION STATUS ANALYSIS IN CEREBROSPLINAL FLUID AND PLASMA OF ADVANCED LUNG ADENOCARCINOMA WITH BRAIN METASTASES

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Background: We aimed to investigate the feasibility of droplet digital PCR (ddPCR) for the detection of epidermal growth factor receptor (EGFR) mutations in circulating free DNA (cfDNA) from cerebrospinal fluid (CSF) and plasma of advanced lung adenocarcinoma (ADC) with brain metastases (BM).

Methods: Fourteen advanced ADC patients with BM carrying activating EGFR mutations in tumour tissues were enrolled in this study, and their matched CSF and plasma samples were collected. EGFR mutations were detected by the Amplification Refractory Mutation System (ARMS) in tumour tissues. EGFR mutations, including 19del, L858R, and T790M, were examined in cfDNA isolated from 2mliliter CSF or plasma by ddPCR assay. The clinical response to EGFR-TKIs was analyzed in 14 patients. Patients achieved partial response (PR) of BM after treated with combination of WBRT and gefitinib (21.4%; one of 19del and two of L858R), and in plasma of six patients (42.9%; 9 L858R, one of T790M, and one of 19del&T790M). All EGFR T790M mutations were found during or after EGFR-TKIs treatments. The three patients with activating EGFR mutations in CSF achieved partial response (PR) of BM after treated with combination of WBRT and gefitinib (19del and T790M).

Conclusion: It was feasible to test EGFR mutation in CSF. CSF may serve as liquid biopsy of advanced ADC with BM by enabling measurement of cfDNA within CSF to characterize EGFR mutations.
**SESSION OA01: RISK ASSESSMENT AND FOLLOW UP IN SURGICAL PATIENTS**
MONDAY, DECEMBER 5, 2016

**OA01.01 INSTITUTIONAL-BASED DIFFERENCES IN THE QUALITY AND OUTCOMES OF NSCLC SURGICAL RESECTIONS**

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**Background:** Institutional-level differences in NSCLC survival are associated with differences in the quality of oncologic care. We examined stage-stratified and overall survival of patients in different categories of US Commission on Cancer (CoC)-accredited institutions, to quantify inter-institutional differences in survival impactful quality measures and estimate their relative survival impact, in order to identify the most impactful targets for improvement efforts. **Methods:** National Cancer Data Base (NCDB) institutions were grouped according to CoC category into: Community Cancer Program (CCP), Comprehensive Community Cancer Program (CCCP), Teaching Research Program (TRP), and NCI Program/Network (NCIP). Resections for stage I-IIA NSCLC in the National Cancer Data Base from 2004-2013 performed within each category of institution were examined for specific quality parameters. Survival was estimated by the Kaplan-Meier method and compared with the log-rank test. **Results:** Of 125,408 NSCLC eligible patients, 8% received surgery at CCP, 52% at CCCP, 28% at TRP, and 12% at NCIP. The pNX rate was 8%, 5.7%, 5.5%, and 3.2% respectively (p < 0.001); the median (IQR) nodal count for pNX1 patients was 6 (7), 7 (7), 8 (9), and 10 (10) respectively, and the CoC quality criterion attainment rate (examination of ≥10 nodes for stage I/II patients) was 25.5%, 30.2%, 38.7%, and 51.4% (p < 0.001). The nodal upstaging rate from clinical (c) N0 to pathologic N-positive was 10.4%, 10.8%, 10.7% and 13.1% (p < 0.001); for cN1, nodal upstaging rate was 9.4%, 10.5%, 10.4% and 15.5% (p < 0.001). There was no significant inter-institutional difference in 5-year OS for stage I/II patients with pNX resections: 0.47 v 0.50 v 0.51 v 0.54 (log-rank p = .27), whereas stage I/II patients with resections meeting or failing the CoC quality standard had persistent inter-institutional survival differences. For those with <10 nodes, 5-year survival was 0.59 v 0.63 v 0.65 v 0.69 (log-rank p < 0.001) and for those with ≥10 nodes, it was 0.62 v 0.64 v 0.67 v 0.69 (log-rank p < 0.001). **Conclusion:** Striking differences in the quality and accuracy of NSCLC pathologic nodal staging exist between the different categories of CoC-accredited facilities. Institutions with higher quality staging have significantly better stage-stratified OS. This inter-institutional survival difference disappears in the patients without examination of any lymph nodes, who arguably have similarly bad quality pathologic nodal staging. However, adjustment for other measures of pathologic nodal staging quality failed to eliminate the inter-institutional survival disparity. Further investigation of inter-institutional practice differences is needed to understand the institutional-level difference in survival after lung cancer surgery.

**Keywords:** Survival disparities, Quality of care, Surgical resection, Staging

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**OA01.02 A LUNG CANCER SURGICAL MORTALITY RISK-PREDICTION ALGORITHM TO INFORM LUNG CANCER SCREENING SHARED DECISION-MAKING**

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**Background:** Low-dose computed tomography lung cancer screening has been demonstrated to increase detection of cases at an early-stage and reduce lung cancer mortality (vs. x-ray or no screening). However, screening benefits are greatly reduced in persons who are poor candidates for curative intent surgery in the event of screen-detected early-stage disease. To date, no practical tools have been developed to assess potential suitability for surgical treatment at the time of screening, to inform shared decision-making. The objective of this study was to use readily available socio-demographic and medical history variables to develop a prediction model that estimates the risk of 30-day mortality following surgical treatment for early-stage non-small cell lung cancer (NSCLC). **Methods:** We used logistic regression to develop a risk-prediction model for 30-day mortality following surgical treatment for Stage I/II NSCLC in patients age 65 to 79 using SEER-Medicare linked databases (2007-2012). Additionally, all patients had at least 1 year of Medicare enrollment prior to NSCLC diagnosis and received initial surgical treatment within 6 months of diagnosis. We developed the model with a training sample of 1,571 surgical cases and conducted internal validation exercises with a sample 4,632 independent surgical cases. Models included age, sex, race, country of birth, urban-rural status, and comorbidities in the year prior to NSCLC diagnosis. **Results:** The Hosmer-Lemeshow test (by decile) and area under the receiver-operating characteristic curve (AUC) were assessed as measures of model calibration and discrimination, respectively. **Conclusion:** This model demonstrated similar performance in women, men, whites, and non-whites; and also showed similar calibration and discrimination for males and females, and non-cancer mortality (vs. x-ray or no screening). However, screening benefits are demonstrated to increase detection of cases at an early-stage and reduce lung cancer mortality (vs. x-ray or no screening).
OA01: RISK ASSESSMENT AND FOLLOW UP IN SURGICAL PATIENTS
MONDAY, DECEMBER 5, 2016 - 11:00-12:30

OA01.05 THE IMPACT OF LUNG AGE ON POSTOPERATIVE COMPLICATIONS IN PATIENTS WITH LUNG CANCER COMBINED WITH PULMONARY FIBROSIS AND EMPHYSEMA
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Background: Postoperative complications after pulmonary resection may cause morbidities such as prolonged hospitalization. Recently, combined pulmonary fibrosis and emphysema (CPFE) has been reportedly linked to a high risk for postoperative complications following lung cancer surgery. Moreover, some studies have claimed that lung age (LA) is associated with postoperative complications. Here we clarify the relationship between LA and postoperative complications in lung cancer patients with CPFE. Methods: Among a total of 1166 consecutive patients who underwent curative resection for lung cancer from January 2004 to April 2016 at the Kitasato University Hospital, Japan, a dataset of 36 patients with CPFE was retrospectively analyzed. Lungs with CPFE were defined based on preoperative chest computed tomography (CT) findings. LA was determined using the methods advocated by the Japanese Respiratory Society. The difference between “real age” (RA) and LA was calculated as “RA−LA,” and patients were classified into three groups: group A, RA−LA ≥ 0 (n = 10); group B, −15 ≤ RA−LA < 0 (n = 13); group C, RA−LA < −15 (n = 13). Results: The average age was 70 (males, 69; females, 73.2) years. Thirty-two patients were male and four were female. Almost all patients were ex- or current smokers. The average postoperative hospital stay was 16 (range, 7-56) days. There were no significant differences in age, gender, smoking history, and postoperative hospital stay among the three groups. The surgical procedures were lobectomy (n = 29), segmentectomy (n = 2), and wedge resection (n = 5). Histologically, the tumors were squamous cell carcinoma (n = 22), adenocarcinoma (n = 9), and other tumors (n = 4). Postoperative complications were arrhythmia (4 cases), hypertension (4 cases), air leakage (3 cases), pneumonia (5 cases), hypoxemia (3 cases), and others (5 cases). There were no significant differences in postoperative complications among the groups (p = 0.09). However, cardiovascular complications in group C were significantly higher than those in the other groups (p = 0.008). There were 26 patients with postoperative acute exacerbation, but there were no significant differences among the groups. Conclusion: LA accurately predicted postoperative cardiovascular complications in lung cancer patients with CPFE.

Keywords: competing risk, lung resection, Comorbidity, Pulmonary Function

OA01.06 EARLY POST-OPERATIVE AMBULATION AFTER THORACIC SURGERY - THE WAVE EXPERIENCE
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Background: The occurrence of minimally invasive thoracic surgery interventions has grown steadily since the early 1990s, yet practice patterns for peri-operative management of these patients has lagged behind technical progress. Our thoracic program has created WAVE (Walking After VATS Experiment) which focuses on a multidisciplinary approach to early ambulation after thoracic surgery. Among our first 3 years of data (July 2010- July 2013) was presented at the 2013 IASLC meeting in Sydney, Australia. In response to the positive comments, we have continued our endeavor and in addition, investigated 30 day outcomes and length of stay for the homogenous subset of anatomic lobectomy. Methods: Data was collected from a single surgeon at a single center and includes all consecutive thoracic surgical patients recovered through the WAVE program from July 2010 - July 2016. We excluded patients undergoing tracheostomy, endoscopic only procedures, and mediastinoscopy. Data was collected prospectively and analyzed retrospectively. Results: From July 2010- July 2016, 1152 patients were included for analysis. Within the 6 year period, 798/1152 patients (69%) walked any distance within one hour of extubation, 945/1152 patients (82%) walked 250 feet at any time while in the PACU, 721/1152 patients (63%) walked 250 feet at any time while in the PACU, 239/290 patients (82%) successfully walked the targeted distance of 250 feet within one hour of extubation and only 5/280 patients (1.7%) were unable to ambulate at all in the PACU. There were no adverse events. The subset of anatomic lobectomies included 290 patients of which 197/290 patients (68%) walked any distance within one hour of extubation, 239/290 patients (82%) successfully walked 250 feet at any time while in the PACU, 175/290 patients (60%) achieved the target distance of 250 feet within one hour of extubation and only 5/280 patients (1.7%) were unable to ambulate at all in the PACU. The rate of 30 day post-operative complications compares favorably with the literature and are as follows: 4.1% atrial arrhythmia, 1.0% pneumonia, 6.6% air leak > 5 days, 0.7% DVT, 0.3% acute renal failure, 0.3% pulmonary embolism, 0% stroke, 0% myocardial infarction, 0.8% re-admission and 0% mortality. Mean length of hospital stay was 1.6 days with a median of 1 day. Conclusion: Our “WAVE” experience reveals that aggressive early ambulation is effective in reducing post-operative complications and shortening length of stay. The platform is simple, reproducible and feasible for any thoracic surgical program. Key features for successful implementation include patient and family engagement, a multi-disciplinary team and administrative support.

Keywords: Thoracic Surgery, Lung cancer resection, Post-operative Recovery, Early Ambulation

OA01.07 ALTERNATIVE FOLLOW-UP METHODS BASED ON RECURRENCE PATTERNS AFTER SURGERY FOR NON-SMALL CELL LUNG CANCER
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Background: There is no consensus for the appropriate follow-up of patients after complete resection of non-small cell lung cancer (NSCLC). Our study was designed to visually represent postoperative recurrence patterns for NSCLC with the use of event dynamics and to optimize postoperative follow-up schedule based on risk factors for recurrence. Methods: A total of 892 patients with NSCLC who underwent complete pulmonary resection were studied. There were 538 men and 291 women with a mean age of 69.2 ± 5 years at the time of operation. The majority of the patients had adenocarcinoma (62.5%), underwent lobectomy (85.9%) and pathological stage IA (47.3%). Event dynamics, based on the hazard rate, were evaluated and only first events
(distant metastases or local recurrence) were considered. The effects of sex, histological type and pathological stage were studied. Results: On non-parametric kernel smoothing, the resulting hazard rate curves indicated that the recurrence risk pattern was definitely correlated to sex, with a sharp peak in the first year for men and broad peak during the 2 to 3 years for women. This finding was also confirmed by the analysis of histological type. Although pathological stage IA patients lacked such a large peak in both sexes during the follow-up period, gender difference was shown in pathological stage IB and stage IIA to IIB patients.

The timing of recurrence by sex

Conclusion: The use of recurrence dynamics allows the times of peak recurrence to be visualized. The hazard rate and the peak times of recurrence differed considerably between genders in pathological stage IB or higher. Postoperative follow-up methods should be based on currently recommended follow-up guidelines, giving adequate consideration to the recurrence patterns, and be modified individually.

Keywords: Non-small-cell lung cancer, postoperative, follow-up, recurrence dynamics

SESSION OA02: NOVEL TARGETS AND BIOMARKERS IN MALIGNANT PLEURAL MESOTHELIOMA
MONDAY, DECEMBER 5, 2016 - 11:00-12:30

OA02.01 THE MICRORNA-15/16 FAMILY REGULATES TUMOUR CELL GROWTH VIA FIBROBLAST GROWTH FACTOR SIGNALS IN MALIGNANT PLEURAL MESOTHELIOMA
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Background: Malignant pleural mesothelioma (MPM) is a highly aggressive, asbestos-related malignancy characterized by poor outcome and limited therapeutic options. Fibroblast growth factor (FGF) signals play important roles in mesothelioma cell growth and malignant behavior and their inhibition leads to reduced tumor growth. MicroRNAs (miRNAs) are conserved noncoding RNAs controlling gene expression via translational repression of target mRNAs. The miR-15/16 family is downregulated in MPM and has noncoding RNAs controlling gene expression via translational repression of target proteins.

Methods: Gene and microRNA expression was determined by RT-qPCR or Taqman Low Density Arrays (TLDAs). Mimics were used for restoring microRNA expression. Stimulation or inhibition of FGF signals or bcl-2 was achieved by recombinant FGF2, siRNAs, or small-molecule inhibitors, respectively. A SYBR green-based proliferation assay and colony formation assays were used to monitor effects on cell growth.

Results: Expression analysis showed a consistent downregulation of target FGF/FGFR genes after transfection with microRNA mimics. Restoration of miR-15/16 led to dose-dependent growth inhibition, which significantly correlated with sensitivity to the specific FGFR1 inhibitor PD166866. Re-expression of microRNAs in combination with FGFR knock-down or pharmacological inhibition resulted in reduced activity, indicating target competition. Combined inhibition of the FGF-axis and bcl-2, another established target of miR-15/16, resulted in enhanced activity. Treatment with recombinant FGF2 further reduced mature as well as pri-microRNA levels and also could prevent/reduce growth inhibition by mimics, but only when added within 24 hours after transfection. TLOA screens after stimulation/inhibition of FGF signals identified regulation of several other miRNAs involved in pathways relevant for tumour growth and aggressiveness. Conclusion: Our data shows that the post-transcriptional repression of FGF-mediated signals contributes to the tumour-suppressor function of the microRNA-15/16 family. Impairing hyperactivated FGF signals as well as the anti-apoptotic protein bcl-2 through the restoration of this miRNA family might serve as a novel therapeutic strategy in mesothelioma.

Keywords: Mesothelioma, MicroRNAs, Fibroblast Growth Factors

OA02.02 GREMLIN-1 IS A KEY REGULATOR OF THE INVASIVE PHENOTYPE IN MESOTHELIOMA
Miao Yin1, Mira Tissari1, Jenni Tamminen1, Irene Viivinkka1, Mikko Ronny1, Kaisa Lehti1, Marko Huuttiainen1, Marjukka Myllarniemi4, Katari Koiv4
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Background: Malignant mesothelioma is an aggressive cancer that develops from mesothelial cells, most often in the pleural lining of the lung. We have previously shown that the BMP inhibitor protein gremlin-1 is highly expressed in mesothelioma and induces a mesenchymal and chemoresistant phenotype in mesothelioma cells. Since mesothelioma tumors are locally highly invasive, we analyzed the role of gremlin-1 in mesothelioma cell migration and invasive growth.

Methods: Primary mesothelioma cells isolated from patient pleural fluid as well as mesothelioma cell lines were used for in vitro studies. Cells were transfected with siRNAs or transduced with lentiviral expression vectors. Invasive growth was analyzed in 3D matrigel or collagen I matrices. mRNA expression was analyzed using a commercial PCR array and quantitative RT-PCR. Migration assays were performed using scratch wound assay or Transwell migration assay with fibronectin or collagen coating. TGF-β and BMP signaling activity was measured with reporter-lucerase assays.

Results: Mesothelioma cells expressing gremlin-1 showed invasive sprouting when tumor cell spheroids were imbedded into 3D collagen matrix. Silencing of gremlin-1 expression significantly reduced invasive growth. In addition, cells overexpressing gremlin-1 gained invasive growth ability. This was associated with increased mRNA expression levels of Slug and matrix metalloproteinases (MMP) as well as reduced expression of E-cadherin. The cells were more migratory and exhibited increased expression of certain integrins, especially the αv subunit. Gremlin-1 induced invasive growth was dependent on MMP activity and associated with increased TGF-β activity. Intrapleural injection of gremlin-1-overexpressing mesothelioma cells isolated from a patient with epithelioid mesothelioma, produced tumors in 2/4 mice over 4 months after injection. Cells transduced with vector only did not produce tumors (0/4). When cells were injected subcutaneously together with matrigel gremlin-1 overexpressing tumors appeared more slowly, but exhibited comparable luciferase signal 2.5 months after injection. However, gremlin-1 tumors showed more local spreading and in contrast to control tumors some also developed metastasis (2/6 mice).

Conclusion: Mesothelioma invades locally and has poor prognosis. We have identified gremlin-1 as an important regulator of mesothelioma chemoresistance and invasive growth behavior. Blocking gremlin function may overcome drug resistance and reduce invasion of mesothelioma.

Keywords: invasive growth, Mesothelioma, gremlin

OA02.03 CIRCULATING FIBROBLAST GROWTH FACTOR 18 IS ELEVATED IN MALIGNANT PLEURAL MESOTHELIOMA PATIENTS - A MULTI-INSTITUTIONAL STUDY
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Keywords: Mesothelioma, MicroRNAs, Fibroblast Growth Factors
MicroRNAs were not significantly different between cell lines and tumours. Corresponding significant upregulation in both xenograft and syngraft tumours compared to mesothelioma cell lines. Only miR-223 showed.

**Results:** Tumour xenografts and syngrafts with those in corresponding cell lines in vivo to validate expression levels of miR-143-3p, miR-214-3p and miR-223-3p in xenograft (AB1) models were established. MicroRNA profiles of xenografts were compared against profiles of their corresponding in vitro syngraft (AB1) models. MicroRNA profiles of xenograft tumours showed significant association to the epithelioid (n=77) histology (P=0.0064). Importantly, MPM patients presenting with FGF18 levels below the median had a significantly longer overall survival when compared to those with high FGF18 levels (median survival 625 versus 387 days, P<0.0038). Data on multivariate analysis, disease-free survival, correlation with other biomarkers and tumour volume will be presented at the conference. Conclusion: Our findings reveal that FGF18 is a promising blood-derived candidate biomarker in MPM. Furthermore, FGF18 may support the histological classification of MPM and the identification of MPM patients with poor prognosis.

**Keywords:** mesothelioma, biomarker, fibroblast growth factors

**OA02: NOVEL TARGETS AND BIOMARKERS IN MALIGNANT PLEURAL MESOTHELIOMA**

**Background:** Malignant pleural mesothelioma (MPM) is an aggressive cancer caused by asbestos exposure with limited therapeutic options. Dysregulated microRNAs play an important role in MPM biology and candidate microRNAs have been investigated as diagnostic and prognostic biomarkers or as potential treatment targets. The role of miR-223 has previously been investigated in MPM tumour cells and was shown to act as a tumour suppressor by regulating cell mobility. Previous research indicated miR-223 to be primarily expressed by myeloid progenitor derived cells during differentiation of granulocytes and monocytes. This suggests miR-223 might have a more significant role in the inflammatory response during tumourigenesis. In this study we aimed to investigate the role of miR-223 using mesothelioma xenografts and syngraft models. Methods: Human and mouse mesothelioma cell line-derived xenografts (MSTO-2101 and H236) and syngraft (AB1) models were established. MicroRNA profiles of xenografts were compared against profiles of their corresponding in vitro cultured cells to determine candidates. RT-qPCR using TaqMan MicroRNA assays was used to validate expression levels of miR-143-3p, miR-214-3p and miR-223-3p in tumour xenografts and syngrafts with those in corresponding cell lines in vitro. Species-specific ddPCR analysis was performed on RNA from xenograft tumours to determine the expression of human and mouse pri-miR-223. Results: MicroRNA profiles of xenograft tumours showed significant upregulation (p<0.001) with only minimal expression levels of human tumour pri-miR-223 within xenograft tumours. Conclusion: Mature miR-223 is significantly overexpressed in xenograft tumours compared to corresponding in vitro mesothelioma cell lines suggesting stromal contribution. Species-specific pri-miRNA confirmed miR-223 is almost exclusively expressed by the mouse stromal cells in xenograft tumours. Ultimately, localising the expression of miR-223 to specific cell types (such as myeloid derived cells) through in situ hybridisation should help identify a more biologically relevant role for miR-223 in the tumour microenvironment.

**Keywords:** Mesothelioma, microrna

**OA02.05 EXPRESSION OF MIR-223 IN MESOTHELIOMA XENOGRAFTS ORIGIYATES FROM STROMAL CELLS IN THE TUMOUR MICROENVIRONMENT**

**Background:** Malignant pleural mesothelioma (MPM) is an aggressive cancer caused by asbestos exposure with limited therapeutic options. Dysregulated microRNAs play an important role in MPM biology and candidate microRNAs have been investigated as diagnostic and prognostic biomarkers or as potential treatment targets. The role of miR-223 has previously been investigated in MPM tumour cells and was shown to act as a tumour suppressor by regulating cell mobility. Previous research indicated miR-223 to be primarily expressed by myeloid progenitor derived cells during differentiation of granulocytes and monocytes. This suggests miR-223 might have a more significant role in the inflammatory response during tumourigenesis. In this study we aimed to investigate the role of miR-223 using mesothelioma xenografts and syngraft models. Methods: Human and mouse mesothelioma cell line-derived xenografts (MSTO-2101 and H236) and syngraft (AB1) models were established. MicroRNA profiles of xenografts were compared against profiles of their corresponding in vitro cultured cells to determine candidates. RT-qPCR using TaqMan MicroRNA assays was used to validate expression levels of miR-143-3p, miR-214-3p and miR-223-3p in tumour xenografts and syngrafts with those in corresponding cell lines in vitro. Species-specific ddPCR analysis was performed on RNA from xenograft tumours to determine the expression of human and mouse pri-miR-223. Results: MicroRNA profiles of xenograft tumours showed significant upregulation (p<0.001) with only minimal expression levels of human tumour pri-miR-223 within xenograft tumours. Conclusion: Mature miR-223 is significantly overexpressed in xenograft tumours compared to corresponding in vitro mesothelioma cell lines suggesting stromal contribution. Species-specific pri-miRNA confirmed miR-223 is almost exclusively expressed by the mouse stromal cells in xenograft tumours. Ultimately, localising the expression of miR-223 to specific cell types (such as myeloid derived cells) through in situ hybridisation should help identify a more biologically relevant role for miR-223 in the tumour microenvironment.

**Keywords:** Mesothelioma, microrna

**OA02.06 CONVERTING TUMOR-MEDIATED PD-L1 INHIBITION INTO CAR-T CELL COSTIMULATION TO POTENTIATE THORACIC CANCERS IMMUNOTHERAPY**

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**Background:** To overcome tumor-mediated inhibition of chimeric antigen receptor (CAR) T cells, we herein investigated the impact of tumor PD-L1 upregulation on CAR T-cell exhaustion and anti-tumor efficacy, and further developed clinically translatable T-cell extrinsic as well as intrinsic strategies to overcome PD-L1 inhibition in models of lung cancer (LC) and malignant pleural mesothelioma (MPM). Methods: Human T cells were transduced with MSLN-specific CAR with CD28 and CD3zeta domains (M28z) were tested in vitro and in clinically-relevant LC and MPM mouse models by bioluminescence imaging, BLI of tumor burden progression. To counteract PD-1/PD-L1 inhibition in vivo, we evaluated the efficacy of PD-1 blocking antibody or cell-intrinsic genetic-engineering strategies by cotransducing M28z CAR T cells with a PD-1 dominant negative receptor (PD1-DNR) or with PD-1/4-1BB fusion protein. Results: A single, low-dose of M28z CAR T cells is able to resist the progression of established tumor for 40 days, but mice eventually died with progressing tumor. Tumor harvest analysis demonstrated the PD-1 and PD-L1 upregulation on CAR T cells and tumor cells (Figure panel A). We then confirmed in vivo that PD-L1 inhibits M28z T-cell effector functions (proliferation, cytotoxicity and cytokine secretion). The addition of PD-1 blocking potentiates CAR T-cell therapy in vivo but its efficacy requires multiple injections (Panel B). In contrast, a single dose of M28z T cells coexpressing PD1-DNR restore effector functions, enhance tumor burden control (Panel C) and prolong median survival (56 vs 82 days, p<0.001). Converting PD-L1 inhibition into a positive costimulatory signal by PD-1/4-1BB construct cotransduction into M28z CAR T cells enhanced cytokine secretion and T-cell accumulation (Panel D).

(See Figures next page)
OA02.07 CHARACTERIZATION OF THE TUMOR MICROENVIRONMENT AND INVESTIGATION OF IMMUNE CHECKPOINT EXPRESSION IN MALIGNANT PLEURAL MESOTHELIOMA
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Background: Malignant pleural mesothelioma (MPM) is an aggressive cancer with a poor prognosis and an increasing incidence, for which novel therapeutic strategies are urgently required. Since the immune system has been described to play a role in protection against MPM, characterization of its tumor immune microenvironment (TME) and immune checkpoints might help to identify new immunotherapeutic targets and their predictive and/or prognostic value. Methods: Immunohistochemistry (IHC) was performed on tissue samples of untreated (n=40) and chemotherapy-pretreated (n=14) MPM patients. Different subsets of immune cells were identified based on staining for CD4, CD8, FoxP3, CD68, CD45RO, and granzyme B. The expression of the immune checkpoints TIM-3, LAG-3, PD-1 and its ligand PD-L1 was also investigated. The relationship between the immunological parameters and survival, as well as response to chemotherapy was analyzed using the R statistical software. Results: All patients had CD8+ tumor infiltrating lymphocytes (TILs), CD68+ histiocytes and macrophages and CD45RO+ T cells in their stroma, with CD8+ TILs being the predominant cell type of the immune infiltrate. Stromal CD4+ TILs were found in 75% of the untreated and 71% of the pretreated samples. A subset of those cells was also FoxP3+ and these CD4+FoxP3+ cells were positively correlated with stromal CD4+ expression (p<0.001). Less than half of the samples showed positivity for granzyme B. Both, untreated and pretreated patients had PD-1+ TILs, while only 10% of the untreated patients also had PD-1+ tumor cells. PD-L1 positivity on lymphocytes and/or tumor cells was observed for more than half of the patients, with significant differences according to the histological subtype (p<0.001). Patients with a sarcomatoid histology showed the most PD-1 expression. TIM-3 was expressed in tumor cells, stromal lymphocytes and plasma cells, less often in pretreated samples compared to untreated samples. All samples were negative for LAG-3. After multivariate analysis stromal CD45RO expression was found to be an independent negative predictive factor for response to chemotherapy (p=0.017) and expression of CD4 and TIM-3 in lymphoid aggregates were good prognostic factors (p=0.008; p=0.001). Conclusion: Our data reveal the diversity of immune cells present in MPM and point to TIM-3 as a new target in mesothelioma. Administering chemotherapy before or together with PD-1/PD-L1/TIM-3 blocking agents may not be the best combination sequence and further research on the predictive value of CD45RO in the stroma might guide patient selection for chemotherapy.

Keywords: Immune checkpoints, tumor microenvironment, biomarkers
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**OA03.02 ATEZOLIZUMAB AS 1L THERAPY FOR ADVANCED NSCLC IN PD-L1-SELECTED PATIENTS: UPDATED ORR, PFS AND OS DATA FROM THE BIRCH STUDY**

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**Background:** Atezolizumab, a humanized anti-PD-L1 mAb, inhibits the PD-L1/PD-1 pathway to restore tumor-specific T-cell immunity, resulting in durable anti-tumor effects. BIRCH (NCT02031468) is a single-arm Phase II study of atezolizumab monotherapy in PD-L1-selected advanced NSCLC patients, across multiple therapy lines. Primary analyses (median follow-up, 8.5 months) demonstrated a meaningful ORR with durable response in chemotherapy-naive 1L and 2L PD-L1-selected patients. Here we report updated efficacy data in 1L patients. Methods: 1L eligibility criteria included PD-L1-selected, advanced-stage NSCLC with no CNS metastases or prior chemotherapy. PD-L1 was centrally evaluated (VENTANA SP142 IHC assay). Patients expressing PD-L1 ≥ 25% of tumor cells (TC) or tumor-infiltrating immune cells (IC), TC or IC ≥25%, were enrolled. Patients with EGFR mutation or ALK rearrangement must have had prior TKI treatment. Atezolizumab 1200mg was administered IV q3w until radiographic disease progression or unacceptable toxicity. The primary endpoint was independent review facility (IRF)-assessed ORR. Secondary endpoints included investigator (INV)-assessed ORR, DOR, PFS (RECIST v1.1) and OS. Results: With a median follow-up of 14.6 months, median OS was not reached in TC3 or IC3 patients and was 20.1 months in TC2 or IC2 (ITT) patients. INV-assessed ORR was 32% and 24%, respectively (Table). Furthermore, ORR was 31% for mutant EGFR (n=13) vs 20% for wild-type EGFR patients (n=104), and 27% for mutant KRAS (n=33) vs 21% for wild-type KRAS patients (n=67). No new safety signals were observed. Updated efficacy (including IRF ORR), safety and exploratory biomarker analyses will be presented. Conclusion: With longer follow-up, atezolizumab continued to demonstrate promising efficacy in 1L NSCLC. Atezolizumab has durable anti-tumor effects in the 1L setting, in EGFR and KRAS mutant and wild-type tumors, and support ongoing Phase III trials evaluating atezolizumab vs chemotherapy in 1L NSCLC.

**OA03.03 JAVELIN SOLID TUMOR: SAFETY AND CLINICAL ACTIVITY OF AVELUMAB (ANTI-PD-L1) IN FIRST-LINE TREATMENT IN PATIENTS WITH ADVANCED NSCLC**

Guy Jerusalem1, Franklin Chen1, David Spiegel1, Nicholas Iannotti2, Edward Mclay3, Charles Redfern4, Jaafar Bennouma5, Matthew Taylor6, Howard Kaufman7, Karen Kelly8, Vikram Chand1, Anja Von Heydebreck9, Claire Verschraegen10


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SESSION OA04: EPIDEMIOLOGY AND PREVENTION OF LUNG CANCER
MONDAY, DECEMBER 5, 2016 - 11:00-12:30

OA04.01 EDUCATIONAL AND WEALTH INEQUALITIES IN TOBACCO USE AMONG MEN AND WOMEN IN 54 LOW-AND-MIDDLE-INCOME COUNTRIES
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Background: To support health policies and place monitoring systems to tackle socio-economic inequalities in tobacco use in low and middle-income countries (LMIC) are seldom reported. We aimed to describe, sex-wise, educational, national and state level of inequalities in tobacco use in 54 low and middle income countries. Methods: We analyzed DHS data on tobacco use collected in 54 countries. We calculated weighted prevalence estimates of current tobacco use (any type of tobacco) in each country for five wealth groups and four educational groups. We calculated both absolute and relative measures of inequality, i.e., the Slope Index of Inequality (SII) and Relative Index of Inequality (RII), which take into account the distribution of prevalence across all wealth and education groups and account for population size. We also calculated the aggregate SII and RII for low-income (LCI), lower-middle-income (LMI) and upper-middle-income (UMI) countries as per World Bank classification. Results: Male tobacco use among was highest in Bangladesh (70.3%) lowest in Sao Tome (7.4%); whereas female tobacco use highest in Madagascar (21%) and lowest in Tajikistan (0.2%). Among men educational inequalities varied widely between countries but aggregate RII and SII showed an inverse trend by country wealth groups. RII was 3.61 (95% CI 3.83-4.61) in LCI, 1.99 (95% CI 1.52-2.30) in LMC, and 1.82 (95% CI 1.21-2.7) in UMI. Wealth inequalities among men varied less between countries but both RII and SII showed an inverse pattern where RII was 2.43 (95% CI 2.02-2.88) in LCI, 1.84 (95% CI 1.54-2.21) in LMCs, and 1.67 (95% CI 1.15-2.42) in UMC. For educational inequalities among women, the RII varied much more than SII varied between the countries, and aggregate RII was 4.93 (95% CI 3.87-9.23) in LCI, 3.05 (95% CI 1.44-6.47) in LMC and 1.58 (95% CI 3.37-5.76) in UMC. Wealth inequalities among women showed a pattern similar to that of men: the RII was 5.88 (95% CI 3.91-8.85) in LCI, 1.76 (95% CI 0.80-3.85) in LMC, and 0.39 (95% CI 0.09-1.64) in UMI. In contrast to men, among women the SII was pro-rich (higher smoking among the more advantaged) in 13 of the 52 countries (7 of 23 LMIC and 5 of 7 UMC). Conclusion: Our results confirm that socio-economic inequalities tobacco use exist in LMIC, varied widely between the countries, and were much wider in the lowest income countries. These findings are important for better understanding and tackling of socio-economic inequalities in health in LMIC.

Keywords: Tobacco use; socio-economic status; health inequalities; low-and-middle-income countries.

OA04.02 SMOKING BEHAVIOR IN PATIENTS WITH EARLY STAGE NON-CELL LUNG CANCER: A REPORT FROM ECOG-ACRIN 1505 TRIAL
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Background: Approximately 85% of lung cancer is related to cigarette smoking. Smoking cessation has been reported to benefit patients even after the diagnosis of lung cancer. We studied the smoking behavior of patients with lung cancer in a phase 3 study for early stage lung cancer. Methods: The ECOG-ACRIN 1505 study enrolled patients with stages IB, II and IIIA non-small cell lung cancer (NSCLC) after they had undergone surgical resection. It was designed to evaluate whether the addition of bevacizumab would improve survival relative to cisplatin-based chemotherapy alone. Smoking cessation was assessed by self-report at baseline and outcomes were a secondary endpoint. Patients completed a questionnaire about their smoking habits at baseline, 3, 6, 9, and 12 months after study entry. Results: Out of 1501 patients enrolled, 99%, 90%, 85%, 82% and 80% responded to the questionnaire at baseline, 3, 6, 9, and 12 months respectively. Nearly 90% reported having smoking during their lifetime. At study entry, 12% reported ongoing smoking. The median age patients started smoking was 17 years and the median age at which they quit smoking was 55 years. The median number of cigarettes smoked per day was 20. Approximately 6% smoked cigars (median number 2/day). Of the 40% that reported smoking after the diagnosis of lung cancer, only 15% reported smoking at 12 months after the diagnosis. Among those who continued to smoke, 79% reported smoking fewer cigarettes/day, whereas 11% smoked more cigarettes. When asked about the number of cigarettes smoked at 12 mos, 63% reported smoking fewer than 10 cigarettes/day. The incidence of grades 2-5 toxicity was 76% in smokers versus 69% in non-smokers (P=0.06). There were no differences in dose reductions for chemotherapy (P=0.55) or bevacizumab (P=0.90) between smokers and non-smokers. The median number of chemotherapies cycles were nearly identical for smokers and non-smokers. The disease-free survival (DFS) and OS for smokers relative to non-smokers were 0.97 (95% CI 0.83-1.15) and 1.5 (P=0.01) respectively. Conclusion: This is the first comprehensive, prospective report of smoking habits of patients with lung cancer. There were a high rate of smoking cessation and reduction in number of cigarettes smoked, that was maintained at 12m after study entry. Toxicity and DFS did not differ significantly between smokers and never-smokers, though overall survival was more favorable with the never-smokers. Study was coordinated by ECOG-ACRIN (Robert L. Comis, M.D., Chair) and supported in part by Public Health Service Grants CA180820, CA180888, CA180821, & CA180863.

Keywords: lung cancer, smoking, tobacco control
OA04: EPIDEMIOLOGY AND PREVENTION OF LUNG CANCER
MONDAY, DECEMBER 5, 2016 - 11:00-12:30

OA04.03 PRELIMINARY RESULTS OF A LOW COST INTERVENTION TO IMPROVE TOBACCO CESSATION PRACTICES WITHIN A LARGE UNIVERSITY HEALTH SYSTEM
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Background: Tobacco cessation is critical for both population and individual health, and especially so in the context of a lung cancer screening program. Our institution initiated formal lung cancer screening in 2013. In preparation for this we audited randomly selected clinic visits to assess adherence to published tobacco cessation guidelines. Our findings in that study prompted us to initiate a systematic multi-step program to improve tobacco practices from assessing tobacco use to prescribing pharmacotherapy, and referral to tobacco cessation counselors. Methods: The project included four separate but related interventions; 1) Inviting clinic directors to send a clinic staff member of their choice for formal training in a specialize Tobacco treatment Specialist (TTS) course. 2) Generating monthly reports showing completeness of tobacco history (Current/Former/ Never), pack-years recording, and (for former smokers) quit dates, use of pharmacotherapy for current smokers, and referrals for either tobacco cessation or formal lung cancer screening. 3) Providing monthly feedback to clinic directors comparing their performance to others in the project, and 4) Initiation of an electronic Best Practice Alert prompt for smokers of tobacco identified by Lung Cancer Screening Questionnaire & decision aid and referral to Tobacco Counselor. Results: This University Health System is affiliated with over 150 satellite clinical sites. 20 sites delivering mostly adult primary care were invited to participate. Individuals from 14 sites completed TTS training. Initial assessment of tobacco use (Current/Former/ Never) was excellent (>99%) across all clinical sites, including those who did not participate in TTS training. However, pack-years were recorded on average less than 40% of the time and quit dates for former smokers were recorded less than 30% of the time at baseline. After training clinic staff in the TTS course, and regular ongoing feedback to clinic directors, we observed a significant initial increase in accurate recording of pack-years and quit dates (two points of emphasis) for all sites involved in the project, as well as referrals to tobacco counselling. Over this time, unfortunately we did not detect an increase in the rate of prescription of tobacco pharmacotherapy. The There was a gradual increase in the the number of referrals for lung cancer screening Cts increased from an average of 30 per month to an average of over 70. Conclusion: This project to disseminate the skills of a TTS training course to clinics within a large University Health System has led to modest improvements in overall practices and demonstrated areas where additional improvements are needed.

Keywords: tobacco cessation, quality improvement, screening

OA04.04 EPIDEMIOLOGY AND PREVENTION OF LUNG CANCER
MONDAY, DECEMBER 5, 2016 - 11:00-12:30

OA04.05 CHRONIC INFLAMMATION, NSAIDS AND THE RISK OF LUNG CANCER DEATH
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OA04.06 EXAMINING PLEIOTROPIC ASSOCIATIONS OF GENETIC RISK VARIANTS FOR CHRONIC OBSTRUCTIVE PULMONARY DISEASE WITH LUNG CANCER RISK
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Background: Tobacco smoke is the primary cause of chronic obstructive pulmonary disease (COPD) and lung cancer, and among smokers, COPD is associated with increased lung cancer risk. However, fewer than 30% of smokers are diagnosed with either disease, suggesting that genetic factors also influence the pathogenesis of both diseases. Despite the plausibility for shared genetic predisposition, knowledge about pleiotropy between COPD and lung cancer is limited. Methods: Using the Genetic Epidemiology Research on Adult Health and Aging cohort established at Kaiser Permanente Northern California (KPNC), an integrated healthcare system, we examined non-Hispanic white patients aged ≥40 years diagnosed with lung cancer (n=449), including those with COPD (n=243) or without COPD (n=176), and neither disease (n=26,553) through January 31, 2014. Those with lung cancer were identified from KPNC Cancer Registry data. Those with COPD were identified from health record data, requiring at least one hospitalization with a principal discharge diagnosis or two outpatient visits with a diagnosis of chronic bronchitis, emphysema, or COPD (ICD-9 codes: 491.1, 492, 496). We examined 16 single nucleotide polymorphisms (SNPs) in 10 risk loci identifies previously for COPD or airflow obstruction and performed widespread association studies (1q4, 4q22, 4q31, 2q32, 6p21.32, 11q22, 14q23, 15q25.1, 16p11.2, 19q13) for their associations with lung cancer risk, overall and stratified by COPD. SNPs were examined individually and also jointly as an unweighted 16-SNP risk score. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using logistic regression, adjusted for age, sex, pack-years of smoking, and principal components of genetic ancestry. Results: Only two SNPs at 15q25.1, a risk locus also known for lung cancer and nicotine dependence, were associated with overall lung cancer risk: rs803419 (per-allele OR=1.22, 95% CI: 1.07-1.39, p=0.003) and rs12943385 (per-allele OR=1.23, 95% CI: 1.08-1.40, p=0.002). In stratified analyses, associations were stronger for lung cancer without COPD (rs803419: OR=1.36, 95% CI: 1.09-1.69; rs12943385: OR=1.24, 95% CI: 1.00-1.54) than lung cancer with COPD (rs803419: OR=1.09, 95% CI: 0.90-1.31; rs12943385: OR=1.17, 95% CI: 0.97-1.40). The 16-SNP risk score was suggestively associated with overall lung cancer risk (1q32.2; lowest quintile (OR=0.80, 95% CI: 0.57-1.76), with the magnitude of association somewhat stronger for lung cancer with COPD (OR=1.28, 95% CI: 0.84-1.79) than without COPD (OR=1.16, 95% CI: 0.72-1.88). Conclusion: Our preliminary results provide minimal evidence of pleiotropic associations of identified genetic variants for COPD with lung cancer risk, although analyses are limited by the number of lung cancer patients examined.

Keywords: lung cancer, pleiotropy, Chronic obstructive pulmonary disease

OA04.06 EPIDEMIOLOGY AND PREVENTION OF LUNG CANCER
MONDAY, DECEMBER 5, 2016 - 11:00-12:30

OA04.07 CLINICAL CHARACTERISTICS OF LUNG ADENOCARCINOMA IN THE YOUNG: RESULTS FROM THE GENOMICS OF YOUNG LUNG CANCER STUDY
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Background: Lung cancer is increasingly recognized as a heterogeneous disease comprised of genetically defined subtypes with distinct targetable genomic alterations. However, it is unknown whether established lung cancer risk factors differ between these genetically distinct subtypes. In this study of the genomics of young lung cancer (GoYLC), we present preliminary results of lifestyle risk factors by specific genomic alteration to better characterize lung cancer in the young. Methods: Beginning in July of 2014, patients diagnosed with a bronchogenic lung cancer under the age of 40 were recruited to the GoYLC study. Informed consent was obtained in-person and virtually (online), allowing patients to participate globally, regardless of proximity to study sites (https://www.openmednet.org/site/alcm-gol). To date, this study has accrued a total of 196 cases, of which 85 are adenocarcinoma (AC), Stage 4 AC is the focus of this analysis. Results: Results: Among the 63 stage 4 AC cases, the most common genomic alterations were ALK rearrangements (n=28; 44% of stage 4 AC cases) and EGFR mutations (n=17; 27%) while the other genomic alterations (n=18; 29%) include ROS1, BCR/AR, HER2, P53, RET and ATM. The prevalence of active smoking and/or exposure to passive smoking was highest among those with ALK (64%), intermediate for those with EGFR (47%) and lowest for those with other genomic alterations (39%). However, the prevalence of only active smoking was lowest among those with ALK (28%), followed by EGFR (35%) and highest for those with other genomic alterations (39%). The majority of patients with ALK rearrangements or EGFR mutations reported no family history of lung cancer (82% and 88%, respectively), compared with 67% among those with other genomic alterations. Conclusion: These preliminary results suggest that lifestyle characteristics and family history in young lung cancer patients may differ by genomic alteration. Passive smoke exposure was more prevalent among those with ALK rearrangements or EGFR

Keywords: lung cancer, pleiotropy, Chronic obstructive pulmonary disease

OA04.08 EPIDEMIOLOGY AND PREVENTION OF LUNG CANCER
MONDAY, DECEMBER 5, 2016 - 11:00-12:30
SESSION OA05: TREATMENT ADVANCES IN SCLC
MONDAY, DECEMBER 5, 2016 - 14:15-15:45

OA05.01 PEMBROLIZUMAB IN PATIENTS WITH EXTENSIVE-STAGE SMALL CELL LUNG CANCER: UPDATED SURVIVAL RESULTS FROM KEYNOTE-028
Patrick Ott1, Enriqueta Felip2, Sandrine Hiret3, Dong-Wan Kim4, Anne Morosky5, Sanatan Saraf5, Bilal Piperedi2, Janice Mehnert6
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OA05.02 ANTI-TUMOR IMMUNITY IS A KEY DETERMINANT OF SCLC SURVIVORSHIP
Farhad Kocarsi1, Simone Terra2, Aqsa Nasrin3, Prasuna Mumpa4, Marie Christiane Aubry5, Joanne Yi6, Nafiseh Janaki7, Aaron Mansfield8, Mariza De Andrade9, Ping Yang9, George Vassmatzis10, Virginia Van Keulen10, Tobias Peikert10
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Background: While the majority of small cell lung cancer (SCLC) patients succumb to their disease within a few months, there is a small group of patients who survive for many years after their diagnosis. Factors contributing to the SCLC long-term survivorship remain largely unknown. Herein, we compare tumors from exceptional survivors (EXS) and patients with the expected outcome (EOP) to determine genomic and immunological determinants of SCLC survivorship. Methods: In the Mayo Clinic tissue registry, we identified surgical blocks from 12 EXS who survived 4 years after surgery and 14 EOP who died we identified surgical blocks from 12 EXS who survived 4 years after surgery and were compared with the expected outcome (EOP) to determine genomic and immunological determinants of SCLC survivorship. (Data to be presented).

Importantly, this analysis lays the groundwork for the development of our more comprehensive epidemiology of young lung cancer study that may identify potential lifestyle and environmental risk factors related to specific genomic alterations.

Keywords: genomic alterations, Young Lung Cancer, clinical characteristics

OA05.03 SINGLE-AGENT ROVALPITZUMAB TESIRINE, A DELTA-LIKE PROTEIN 3 (DLL3)-TARGETED ANTIBODY-DRUG CONJUGATE (ADC), IN SMALL-CELL LUNG CANCER (SCLC)
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Background: SCLC is one of the most deadly malignancies. Rovalpituzumab tesirine (SC1817, Rova-T) is a first-in-class ADC directed against DLL3, a novel target identified in tumor initiating cells and expressed in over 80% of SCLC cases. Methods: Seventy-four patients with progressive SCLC after at least one previous systemic therapy were enrolled in a first-in-human study (NCT01901653), irrespective of DLL3 expression, including 68 at active doses of 0.2-0.4 mg/kg administered intravenously every 3 or 6 weeks. Available archived tumor tissue (n=48) was assessed retrospectively by immunohistochemistry for DLL3. Results: Among 60 evaluable subjects, active dose levels resulted in a confirmed objective response rate (ORR) of 18% and a confirmed clinical benefit rate (CBR; stable disease or better) of 68%. Among 26 evaluable subjects with DLL3 expression in at least 50% of tumor cells (DLL3-high), confirmed ORR and CBR were 39% and 89%, respectively. Median duration of response was 5.6 months. One-year survival rates among all and DLL3-high subjects were 18% and 32%, respectively. Among primary sensitive relapse patients, confirmed ORR and CBR among all subjects were 24% (9/38) and 67% (22/33); and among DLL3-high subjects were 53% (8/15) and 100% (15/15), with one-year survival rates of 17% and 33%, respectively. Among primary resistant/refractory relapse patients, confirmed ORR and CBR among all subjects were 12% (3/25) and 72% (18/25); and among DLL3-high subjects were 18% (2/11) and 73% (8/11) with one-year survival rates of 21% and 29%, respectively. The most common grade 3 or higher toxicities included thrombocytopenia (12%), serosal effusions (11%), and skin reactions (8%). ADC pharmacokinetics were linear with a terminal half-life of 10-14 days and anti-therapeutic antibodies did not develop. Conclusion: Rovalpituzumab tesirine demonstrates encouraging single-agent anti-tumor activity with a manageable safety profile, including among patients with disease resistant or refractory to primary chemotherapy. Further development of rovalpituzumab tesirine in SCLC is warranted.

Keywords: clinical trial, Rovalpituzumab tesirine, Delta-like protein 3, SCLC

OA05.05 RANDOMIZED PHASE 2 STUDY: ALSERTIB (MLN8237) OR PLACEBO + PACLITAXEL AS SECOND-LINE THERAPY FOR SMALL-CELL LUNG CANCER (SCLC)
Taofeek Owonikoko1, Kristaana Nackaets2, Tibor Cosszi3, Gyula Ostoros4, Christina Bank5, Claudia Dansky Ullmann6, Erin Zagadalov7, Emily Shieldon-Wanga1, Dirk Huebner8, E Jane Leonard9, David Speigel10

Background: Alisertib, an investigational selective Aurora A kinase inhibitor, showed single-agent antitumor activity in preclinical in vivo SCLC models and was synergistic with paclitaxel in this setting. We report the efficacy,
quality of life (QoL), and safety from this study. Methods: Patients ≥18 years with SCLC relapsed <180 days after standard first-line platinum-based chemotherapy were randomized 1:1 to alisertib 40 mg orally twice-daily on days 1–8, 15–17, or placebo. Survival, response, QoL, and safety results are presented in the Table. The analysis of PFS using IVRS stratification favored Arm A, as did the analysis per corrected stratification factors. Mean EORTC QLQ-C30 QoL scores were similar between arms, as were mean change-from-baseline values at end of treatment (5.7 in Arm A vs 4.9 in Arm B).

Background: A significant proportion of limited-stage small cell lung cancer are elderly. However, there is paucity of data on the efficacy and safety of concurrent chemo-radiotherapy in the elderly to guide treatment decision-making.

Methods: Data from the CONVERT trial was retrospectively analysed to compare the outcome of patients 70 years or older to patients younger than 70 years. Patients were randomised 1:1 to receive 45Gy in 30 twice-daily fractions over 3 weeks or 66Gy in 33 once-daily fractions over 6.5 weeks starting on day 22 of cycle 1 chemotherapy (4 to 6 cycles of Cisplatin 25mg/m2 days 1-3 or Etoposide 100mg/m2 days 1-3, followed by Prophylactic Cranial Irradiation if indicated. Radiotherapy planning was with a 3D conformal technique or intensity modulated radiotherapy. Results: Of 547 patients randomised between April 2008 and November 2013, 57 patients were excluded for the purposes of this analysis as they did not receive concurrent chemo-radiotherapy. Of the 490 included patients, 67 (13.7%) were age 70 years or older with median age of 73 years (70-82). Patients’ characteristics were well balanced apart from more male in the elderly group (p=0.02). There was no significant difference in the number of chemotherapy cycles administered in the two groups (p=0.24). A higher proportion of patients received 30 or 33 fractions of radiotherapy as per protocol in the younger group (85% vs. 73%; p=0.03). Neutropenia grade 3/4 occurred more frequently in the elderly group (84% vs. 70%; p=0.02) but there was no statistically significant difference in neutropenic sepsis (4% vs. 7%; p=0.07) and non-haematological acute/late toxicities. There were two vs. six treatment-related deaths in the elderly and younger group respectively. Concurrent chemo-radiotherapy with modern radiotherapy techniques is a treatment option for elderly patients with good performance status.

Keywords: Radiotherapy, small cell lung cancer, elderly.

OA05.07 PROGNOSTIC VALUE OF CIRCULATING TUMOUR CELLS IN LIMITED-DISEASE SMALLCELL LUNG CANCER PATIENTS TREATED ON THE CONVERT TRIAL

Fabiola Fernandez-Gutierrez, Victoria Foy, Katy Burns, Jackie Pierce, Karen Morris, Lynsey Priest, Jonathan Tugwood, Linda Ashcroft, Corinne Faivre-Finn, Caroline Dive, Fiona Blackhall

Clinical & Experimental Pharmacology Group, CRUK Manchester Institute, Manchester/United Kingdom, 1The Christie NHS Foundation Trust, Manchester/United Kingdom, 1Institute of Cancer Sciences, University of Manchester, Manchester/United Kingdom, 1Manchester Academic Health Science Centre Trials Coordination Unit, Manchester/United Kingdom, 1Department of Clinical Oncology, Univ. of Manchester and the Christie NHS Foundation Trust, Manchester/United Kingdom, 1Univ. of Manchester and the Christie NHS Foundation Trust, Manchester/United Kingdom.

Background: Circulating tumour cells (CTCs) are prevalent in patients with small cell lung cancer (SCLC) (Hou et al, JCO 2012) but their clinical utility is not known for patients with limited disease (LD) who receive concurrent chemoradiation. Here we report on a patient subgroup who underwent CTC analysis and treatment on the Concurrent OnCce-daily (OD) Versus Twice-daily (BD) RadioTherapy (CONVERT) trial (Faivre-Finn Proc. ASCO 2016) that demonstrated a non-significant difference in the primary endpoint of two-year survival for the OD (53%) and BD (56%) arms. Methods: Blood samples (7.5mls) were collected at baseline, prior to any treatment from patients who were enrolled to the CONVERT trial at The Christie Hospital site, Manchester, UK. CTCs were enumerated prospectively using the Cellsearch platform. Patients were randomised 1:1 to receive 45Gy in 30 twice-daily fractions over 3 weeks (Arm 1) or 66Gy in 33 once-daily fractions over 6.5 weeks (Arm 2) starting on day 22 of cycle 1 chemotherapy (4 to 6 cycles of Cisplatin 25mg/m2 days 1-3 or Etoposide 100mg/m2 days 1-3, followed by Prophylactic Cranial irradiation if indicated. Radiotherapy planning was with a 3D conformal technique or intensity modulated radiotherapy. Staging by Positron Emission Tomography (PET) was performed. Standard statistical methods were used to examine associations between CTC number and outcome.

Results: Of 515 patients randomised between April 2008 and November 2013, 79 patients (41 in Arm 1 and 38 in Arm 2) underwent CTC enumeration (CTC subgroup). The clinical demographics and median overall survival (OS) of the CTC subgroup did not differ significantly from the overall study population. The median number (range) of CTCs per 7.5mls blood for all 79 patients was 1 (0-3750) and for arm 1 and arm 2 patients respectively, 12 (0-164) and 158 (0-3750) (p=0.495). There was a trend for association of CTC# with OS (p=0.07) and non-haematological acute/late toxicities. There were two vs. six treatment-related deaths in the elderly and younger group respectively. Concurrent chemo-radiotherapy with modern radiotherapy techniques is a treatment option for elderly patients with good performance status.
with higher TNNM stage. CTc was significant for survival in univariate and multivariate analysis. The median (95% CI) OS for ≥t5 CTc (n=18) was 6.01 (4.2-11.5) months compared to 30.77 (19.7-39.3) months for < 15 CTc (n=62), p <0.001. The positive predictive value of CTc ≥5 for survival > 2 years is 100%, and ≤ 1 year is 72%. CTc also predicted for worse outcome in patients who had undergone PET staging. Conclusion: CTc is highly prognostic for poor survival in patients with LD-SCLC, treated with concurrent chemoradiotherapy, and could aid treatment decision making for this disease.

Keywords: SCLC, Circulating Tumor Cells, chemoradiation, biomarker

SESSION OA06: PROGNOSTIC & PREDICTIVE BIOMARKERS
MONDAY, DECEMBER 5, 2016 - 14:15-15:45

OA06.01 CLINICAL UTILITY OF CIRCULATING TUMOR DNA (CTDNA) ANALYSIS BY DIGITAL NEXT GENERATION SEQUENCING OF OVER 5,000 ADVANCED NSCLC PATIENTS
Philipp Mack 1, Kimberly Banks 1, Jonathan Riess 1, Oliver Zill 2, Stefanie Mortimer 1, Darya Chudova 3, Justin Odegaard 4, Christine Lee 4, Rebecca Nagy 4, Helmy Eltooky 4, Amrali Talazaz 4, Richard Lannman 5, David R. Gandara 1
1 Internal Med, UC Davis Cancer Center, Sacramento/CA/United States of America, 2 Guardant Health, Redwood City/CA/United States of America

Background: Detection of actionable genomic alterations is now required for NCCN guideline-compliant work-up of NSCLC adenocarcinoma. Next-generation sequencing (NGS) of ctDNA, if sufficiently sensitive and specific, could provide a non-invasive, comprehensive genotyping platform relevant to clinical decision-making when tissue is insufficient or at time of progression on targeted therapies. Methods: A highly accurate, deep-coverage (15,000x) ctDNA plasma NGS test targeting 54-70 genes (Guardant360) was used to genotype 5269 advanced-stage NSCLC patients accrued between 6/2014 – 4/2016. The frequency and distribution of somatic alterations in key genes were compared to those described in TCGA (Pearson and Spearman correlations). The clinical impact of ctDNA testing was evaluated by identification of resistance mechanisms emerging at progression on targeted therapy. Results: ctDNA alterations were detected in 86% of cases, and additional driver mutations detected by ctDNA at baseline in 362 consecutive NSCLC patients with tissue mutation data available. The positive predictive value (PPV) of ctDNA sequencing was assessed in 229 patients with known tumor driver alterations. Results: ctDNA alterations were detected in 86% of cases, EGFR mutations in 25%, KRAS mutations in 17%, MET amplification in 4%, BRAF mutations in 3% and other rare but potentially actionable alterations in 9%. Pattern mutations among driver oncogenes were highly consistent with those from TCGA (Pearson r=0.92, 0.99, 0.99 for EGFR, KRAS, and fusion breakpoint location). PPV of ctDNA-detected variants was 100% for EGFR L858R, 98% for EGFR T790M, 96% for ALK, RET, or ROS1 fusions, and 100% for KRAS G12C mutations. In 362 cases with tissue information available, 63% (229/362) were tissue quantity-insufficient or undergenotyped (QNS/UG). ctDNA analysis identified driver mutations in 51 of the 229 QNS/UG cases, a 38% increase in detection rate over tissue alone. Among 1111 EGFR-mutant cases, resistance mutations were identified at progression in frequencies consistent with published literature: EGFR L858R 47%, MET amp 5%, ERBB2 amp 5%, EGFR T790M 0.4%, ALK/other fusions 1%, BRAF mutations 1.8%, PTEN inactivation 2.5%, NFI inactivation 3%, RAI1 inactivation 3%, KRAS mutations 1.5%. In 143 consecutive NSCLC patients with detailed follow-up and serial analysis seen at the UC Davis Cancer Center, informative driver mutations were observed in 68 (43%). Conclusion: This series represents the largest NSCLC ctDNA study to date. Genotypic patterns of truncal mutations were highly consistent with TCGA in terms of frequency and distribution. At baseline, ctDNA augmented the analysis by identifying additional, actionable mutations when tissue was QNS/UG. ctDNA NGS at progression identified emergent resistance mutations that could inform subsequent courses of therapy.

Keywords: liquid biopsy, ctDNA, NSCLC

OA06.03 TRANSCRIPTOME ANALYSIS OF ATM-DEFICIENT NSCLC
Lars Petersen 1, Emeka Enwere 1, Michele Kono 1, Olga Kovalchuk 2, D. Gwyn Bebb 1
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Background: Current targeted therapy options in lung cancer, such as EGFR and ALK inhibitors, are effective, though limited in use by the low percentage of patients that carry targetable mutations for these biomarkers. Targeting a broader biological process like DNA damage response (DDR), as with recent synthetic lethality exploits in BRCA-deficient tumours, may offer a form of precision therapy for a larger number of patients. We have shown that NSCLC cells deficient in the DDR protein ATM, exhibit similar synthetic lethality when treated with a PARP1 inhibitor, and that NSCLC patients lacking detectable ATM have poorer overall survival. In vitro, ATM deficient, or “ATMi” cells show increased sensitivity to chemotherapeutics at much lower levels when given in combination with PARP inhibitor. This data suggests that ATM status may be an important determinant for treatment modalities including low-dose radiation or platinum-based novel signal targeting therapies. Here, we seek to determine the cause of ATM loss in NSCLC patients through targeted sequencing, and thorough transcriptomic and epigenetic analysis.

Methods: We perform whole-transcriptome analysis on NSCLC patient samples previously characterized as normal or ATMic, to detect differences in intracellular pathway activation that lead to different drug sensitivity. Using OncoFinder software identifies possible effective therapies based on which signalling pathways are most active in the normal or ATMi cancer cells. We also perform targeted NGS on these samples. To our knowledge, no sequencing of ATM has been performed on samples that have also been characterized by other methods (i.e. quantitative IHC) to be ATM deficient. Results: We have generated a substantial body of evidence showing that ATM loss has significant impact on the cell sensitivity to several therapeutic modalities. As such ATMic tumours may be treated more effectively using specific treatment strategies than their ATM competent counterparts. Initial analysis of

OA06.02 MUTATIONAL LOAD PREDICTS SURVIVAL IN LDCT SCREENING-DETECTED LUNG CANCERS
Grazzella Soppi 1, Carla Verdi 1, Cristina Borzi 1, Todd Holsher 2, Matteo Dugo 2, Andrea Devecchi 1, Katherine Drake 2, Stefano Sestini 2, Paola Suontoi 2, Elisa Romeo 1, Marco Boeri 1, Ugo Pastarino 1
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Background: The issue of overdiagnosis in low-dose computed tomography (LDCT) screening trials for lung cancer has to be addressed by the development of complementary biomarkers able to improve detection of aggressive disease. We previously identified a 24 plasma miRNA signature endowed with good performance in terms of sensitivity and specificity in subjects enrolled in independent LDCT screening trials. However, the relationship between circulating miRNAs in plasma and the molecular heterogeneity of the patients’ tumours needs to be considered. As such ATMic tumours may be treated more effectively using specific treatment strategies than their ATM competent counterparts. Initial analysis of
CARCINOGENESIS PATHWAYS DRIVE THE PROGNOSIS OF SQUAMOUS CELL LUNG CARCINOMA (SQCLC)

Sara Pilotto, Michele Simbolo, Isabella Spederuti, Silvia Novello, Caterina Vicentini, Umberto Peretti, Serena Pedron, Roberto Ferrara, Mario Caccese, Michele Miliella, Andrea Maffinici, Paolo Visca, Marco Volante, Francesco Facciolli, Antonio San, Luca Carbone, Matteo Brunelli, Marco Chilosi, Aldo Scarpa, Giampaolo Tortora, Elio Brai

1Medical Oncology, University of Verona, Verona/Italy, 2Arc Net Applied Research on Cancer Center, University of Verona, Verona/Italy, 3Regina Elena National Cancer Institute, Rome/Italy, 4Department of Oncology, University of Tum, Aoa San Luigi, Orobasso/Italy, 5Department of Pathology and Diagnostics, University of Verona, Verona/Italy

Background: We previously built and validated a risk classification model for resected SqCLC by combining clinicopathological predictors to discriminate patients’ (pts) prognosis (Pilotto JTO 2015). Here we (AIRCMFAG project no. 14282) investigate the molecular portrait of prognostic outpatients to identify differentially expressed, potentially druggable alterations. Methods: Based on the published 3-class model, 176 and 46 pts with good and bad prognosis, respectively, were identified. Somatic Mutations (SM) and Copy Number Alterations (CNA) were evaluated with Next Generation Sequencing (NGS) for 59 genes (Ion Proton system, Ion Ampliseq custom panel). Moreover, RNA expression assays, immunohistochemistry (IHC) and immunofluorescence (FISH) were performed. Descriptive statistic was adopted and continuous variables were dichotomized according to AUC or medians.

Results: Herein, the analysis of 60 pts (good/poor 27/33) is reported. In the overall population, the median rate of SM (3.3%) is lower compared to the median rate of CNA (28.3%), without significant differences between the two prognostic groups. The most frequent SM resulted to be missense (66.7%) and nonsense (20.3%) mutations, whereas the copy number gain is the most common CNA (76.7%). The distribution of relevant alterations in the main carcinogenesis pathways in term of SM, CNA and expression (by RNA, IHC and FISH), according to the prognostic subgroups, are reported in the table.

Pathway | Gene [method] | Good [%] | Poor [%] | p-value
--- | --- | --- | --- | ---
Squamous differentiation | SOX [CNA] | 74.1 | 51.5 | 0.11
 | TP63 [CNA] | 37.0 | 21.2 | 0.25
Epithelial to mesenchymal transition | SNA1 [RNA] | 59.2 | 90.9 | 0.006
 | Vimentin RNA | 44.4 | 69.7 | 0.07
mTOR | PI3KCA [SM] | 0 | 9.0 | 0.24
 | RICTOR [CNA] | 3.7 | 27.3 | 0.017
 | p-mTOR [IHC] | 11.1 | 18.1 | 0.5
Tyrrosine kinase receptors | DDR2 [SM] | 11.1 | 0 | 0.085
 | FSR2 [RNA] | 3.7 | 18.1 | 0.12
 | MET [FISH] | 11.1 | 24.2 | 0.32
 | FGFR3 [FISH] | 25.9 | 42.4 | 0.28
Cell cycle regulators | CDKN2A [CNA] | 22.2 | 3.0 | 0.38
 | SMAD4 [CNA] | 33.3 | 57.6 | 0.074
Immune checkpoints | PD-L1 [IHC] | 18.5 | 6.1 | 0.23
 | PD-1 [RNA] | 51.8 | 93.9 | <0.001

Conclusion: Although performed on a limited number of pts, such comprehensive analysis of DNA, RNA and proteins, using different methodologies, is feasible and allow identifying potentially druggable prognostic modulators, such as RICTOR/PI3K/mTOR signaling pathway. The possibility to inhibit this pathway with selective agents is currently under investigation in in vitro preclinical models.

Keywords: squamous lung cancer, Prognosis, NGS

OA06.07 EVALUATING GENOMIC SIGNATURES PREDICTING VELIPARIB SENSITIVITY IN NON-SMALL CELL LUNG CANCER (NSCLC)

Lei He, Xin Huang, Yan Sun, Vasudha Sehgal, Xin Lu, Fang Jiang, Paul Jung, Youping Deng, Joann Palma, Anahita Bhatena, Peter Ansell, Mark Mckee

OA06.05 PROTEOMIC ANALYSIS OF ERCC1 PREDICTS BENEFIT OF PLATINUM THERAPY IN NSCLC: A REEVALUATION OF SAMPLES FROM THE TASTE TRIAL

Jean-Charles Soria, Ken Olauussen, Fabiola Cecchi, Eunkyung An, Christina Yau, Marie Wislez, Gérard Zalcman, Denis Moro-Sibilot, David Perol, Franck Morin, Benjamin Besse, Todd Hemmobj

OA06.06 DRUGGABLE ALTERATIONS INVOLVING CRUCIAL PARAMETERS IN SMALL BIOPSIES FROM THE TASTE TRIAL

S136
Background: Veliparib is a potent poly(ADP-ribose) polymerase (PARP) 1 and PARP-2 inhibitor that has synthetic lethality interaction with cancers harboring homologous recombination deficiency. In preclinical models, it has also been shown to delay the repair of DNA damage induced by chemotherapy (platinum, alkylators, topoisomerase inhibitors). Clinically meaningful improvements in progression-free survival and overall survival were observed in a phase 2 trial of veliparib with carboplatin/paclitaxel in previously untreated metastatic or advanced NSCLC (M10-898 study). Intriguingly, smoking history had a major impact on veliparib effect—smokers benefited most from veliparib addition. The underlying mechanism for this observation remains unclear. The efficacy benefit of veliparib in smokers is not dependent on tobacco exposure during study treatment, but correlates with the duration of smoking history, suggesting a genetic basis. Methods: Genomic signatures in NSCLC associated with smoking status have been identified by The Cancer Genome Atlas (TCGA) Lung Cancer Project. Relevant observations were leveraged in the reported analysis. To comprehensively identify genes or genomic features that are associated with smoking status and veliparib response, patient tumor samples from the M10-898 trial were subjected to whole-exome (N = 38) and RNA sequencing (N = 75) analysis. Alexandrov somatic mutational signature was calculated from exome sequencing data. Results: Data from TCGA show that cancer genomes in smokers harbor significantly more genetic alterations than those in non-smokers. These alterations include high mutational burden, high C>A transversion, high mutation frequency of key cancer genes (particularly TP53), and high homologous recombination deficiency. Similar observations were confirmed in the M10-898 study. Of the 38 patients with exome data, 26 were determined to be positive for a smoking-related signature—signature 6. Elevated mutational burden was observed among current and former smokers, with a mean of 199 somatic mutations in current or former smokers (p = 0.004). The small sample of our genomic cohort nevertheless precludes conclusive association of genomic signatures and veliparib benefits. Conclusion: Cancer genomes in smokers are enriched with genetic alterations associated with poor outcome using standard chemotherapy, as well as with vulnerability factors that can prime tumors to respond to veliparib. For further validation, a targeted sequencing assay to detect key DNA damage and repair genes as well as key genomic signatures has been established and will be used in all phase 3 veliparib trials.

Keywords: smoking status, veliparib, whole-exome sequencing, non-small cell lung cancer (NSCLC)

SESSION OA07: LYMPH NODE METASTASES AND OTHER PROPENSITY FACTORS FOR LOCAL SPREAD
Monday, December 5, 2016 - 14:15-15:45

OA07.01 INCIDENCE, LOCAL DISTRIBUTION AND IMPACT OF PN2 SKIP METASTASIS IN PATIENTS UNDERGOING CURATIVE RESSECTION FOR NSCLC
Ariane Steindl, Sabrina Tahan, Mai Nguyen, Balazs Dome, Viktoria Laszlo, Walter Klepetko, Mir Hoda, Thomas Klikovits Division of Thoracic Surgery, Medical University Vienna, Vienna/Austria

Background: The presence of N2 lymph node (LN) involvement has strong impact on therapy and prognosis in non-small cell lung cancer (NSCLC). N2 LN metastasis may occur by skipping LN stations (N2skip-met). We aim to analyze incidence, local distribution and impact of N2skip-mets in a large cohort of patients undergoing curative resection for NSCLC. Methods: A retrospective non-interventional single-center cohort study was conducted, assessing all patients undergoing curative resection for NSCLC between 2006 and 2013 at our institution by reviewing medical charts. Incidence of N2skip-mets among these patients was the primary endpoint. Subsequent secondary correlation of clinical parameters was performed using uni- and multivariable logistic and cox regression models. Results: In total, 1101 patients were enrolled, with the following pathological LN status: 789 (71%) pN0, 211 (19%) pN1, 105 (9.5%) pN2, 5 (0.5%) pN3. Histological subtypes were 789 (71%) adenocarcinoma, n=672 (60%) adenocarcinoma, n=309 (28%); other, n=126 (11%). Incidence of N2skip was 55% (47/105). N2skip-mets occurred more frequently in right sided tumors (odds ratio (OR) 2.14, p=0.058) and patients with adenocarcinoma (vs. other, OR 1.54, p=0.19). Presence of N2skip-mets did not correlate with tumor size (ROC, area under curve (AUC) 0.44, p=0.32). Strikingly, presence of N2skip-mets was significantly increased in smokers (OR 3.5, 95% CI 1.38-8.83, p=0.006). Moreover, patients with N2skip-mets were more likely to develop subsequent brain metastases (OR 4.13, p=0.06). Overall- and recurrence free survival will be presented at the conference. Conclusion: N2skip-mets occur in a high number of patients with N2 disease, with distinct differences in clinicopathologic features. Considering the results of this study, subclassification of N2 disease as recently proposed by the IASLC may have clinical impact in patients with resectable NSCLC.

OA07.02 OMITTING INTRAPULMONARY LYMPH NODE RETRIEVAL MAY AFFECT THE ONCOLOGICAL OUTCOME OF PN0 LUNG CANCER PATIENTS: A PROPENSITY SCORE MATCH ANALYSIS
Xing Wang1, Nan Wu1, Shi Yang2, Chao Lu1, Shaolei Li1, Yuzhao Wang1, Jia Li1, Lijian Zhang1, Yue Yang1
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Background: Clinical practice involving segmental nodes (No.13) and subsegmental nodes (No.14) retrieval for pathological examination varies during lung cancer surgery. This study aims to evaluate whether omitting No.13 and No.14 node retrieval could lead to an inferior oncological outcome for pN0 non-small cell lung cancer (NSCLC) patients. Methods: This retrospective study analyzed 442 cases of NSCLC, both treating with R0 resection and systematic mediastinal lymphadenectomy and confirming as pN0 on postoperative pathology. Study group defined cases whose N1 nodes investigation involving from No.10 to No.14 in pathological report. In Control group, N1 nodes investigation only include No.10 to No.12. Clinical and pathological parameters of above two groups were balanced by propensity score matching based on surgical outcome and the oncological outcomes between two groups were assessed by log-rank test. Results: Seven cases were lost during follow up and 435 cases entered final analysis (Study group, n=170 vs. Control group, n=265). A total of 5.0±3.0 nodes per case were collected from No.13 and No.14 in Study group, which included 3.1±1.9 nodes of No.13 and 2.0±2.2 of No.14. Tumor-located stations harbored 2.8±2.2 lymph nodes, compared to 2.2±2.3 from non-tumor located stations (p=0.006). After propensity score matching, 143 cases remained in each group. Overall survival (OS) and disease-free survival (DFS) were improved in Study group compared with Control group (the 5-year OS rates, 89.3% vs. 77.4%, p=0.027; the 5-year DFS rates, 81.4% vs. 67.4%, p=0.011, FigureA1,1B). In multivariate analysis, T staging and performing intrapulmonary node collection were the prognostic factors for pN0 cases. For the whole cohort, patients with two intrapulmonary stations collected showed better survival than those with zero intrapulmonary station retrieved (Figure4C, 1D). Conclusion: Inferior oncological outcomes of pN0 cases without intrapulmonary node retrieval suggests this procedure may play a role in outcome evaluation for pN0 NSCLC patients.

Keywords: intrapulmonary lymph node, lung cancer, propensity score matching, outcome

OA07.03 PROGNOSTIC SIGNIFICANCE OF MICROMETASTASES IN MEDIASTINAL LYMPH NODES OF PATIENTS WITH RADICALLY RESECTED NON-SMALL CELL LUNG CANCER
Paweł Gwóźdź1, Monika Pasieka-Lis2, Katarzyna Kołodziej3, Juliusz Pankowski4, Marcin Zieliński3
1Thoracic Surgery, Pulmonary Hospital, Zakopane/Poland, 2Pathology Department, Pulmonary Hospital, Zakopane/Poland, 3Thoracic Surgery Department, Pulmonary Hospital, Zakopane/Poland

Background: Recurrence occurs in 30-50% of patients operated for early stage non-small cell lung cancer (NSCLC), what suggests the existence of occult metastases at the time of surgery. Preoperative detection of occult micrometastases in mediastinal lymph nodes could contribute to better selection of patients appropriate for surgery. This retrospective study was undertaken to determine the prognostic significance of preoperatively detected mediastinal lymph node (LN) micrometastases in patients treated with radical surgical resection for stage I and II NSCLC. Methods: From January 2007 to December 2010, 82 patients with stage I and 67 patients with stage II NSCLC underwent transcervical extended mediastinal lymphadenectomy (TEMLA) and subsequent radical pulmonary resection. A total of 4841 mediastinal lymph nodes resected during TEMLA procedure and determined as metastases-free by hematoxylin and eosin staining were labelled to detect occult micrometastases (dual immunohistochemical staining with AE1/AE3 and BerEP4 antibodies). Results: Micrometastases were detected in mediastinal LN of 16 patients (9.7%). 11 patients had only one LN station affected (68.8%). Subcarinal LN were most frequently affected.
Abstracts
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OA07.05 PROGNOSTIC IMPACT OF PLEURAL LAVAGE CYTOLgy (PLC): SIGNIFICANCE OF PLC AFTER LUNG RESECTION
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Background: We previously reported the prognostic significance of pleural lavage cytology (PLC) in patients undergoing surgery for non-small-cell lung cancer (NSCLC). Based on a larger cohort of more than 3500 NSCLC patients, which is the largest ever reported from a single institution in the literature, we evaluated the prognostic impact of PLC on survival and recurrence.

Methods: From January 1993 to July 2015, 3671 patients underwent R0 surgical resection for NSCLC at our institution and PLC results before (pre-) and after (post-) lung resection were both available. The cytological evaluation was classified into 3 categories: negative (-), suggestive (+), positive (++). We included 771 patients whose PLC results were suggestive, and 3594 patients were analyzed. The impact of PLC results on survival and recurrence was evaluated with conventional clinicopathological factors.

Results: The overall survival (OS) of pre-PLC (+) patients was significantly inferior to that of pre-PLC (-) patients. However, the 5-year OS rate of pre-PLC (+) patients was 43%, which was significantly better than that of patients with pleural dissemination (11%). In the following analyses, we divided the patients into 3 groups according to pre-/post-PLC results as follows: Pre (+)/post (-), Group A (n=3461); pre (+)/post (+), Group B (n=43); and post (+), Group C (n=87). Statistically significant difference was not observed between Groups A and B in OS or in recurrence-free survival (RFS) (p=1.00, 0.28, respectively). However, there were significant differences in OS and RFS between Groups B and C (p=0.01 and p=0.02), and between Groups A and C (p=0.01 and p=0.01, respectively). In univariate and multivariate analyses of clinicopathological factors including post-PLC results to identify prognosticators for OS, post-PLC (+) hazard ratio (HR) =2.20, p<0.01), older age (>65 years; HR=1.95, p<0.01), smoking history (+) (HR=1.48, p<0.01), elevated serum CEA level (>5.0 mg/dL; HR=1.28, p<0.01), pathologically2 (HR=1.28, p<0.01), pN1 (HR=1.48, p<0.01), StageII (HR=1.51, p<0.01), pN1+p (HR=1.43, p<0.01), lvy (HR=1.32, p<0.01), and v (HR=1.53, p<0.01) were found to be significant independent unfavorable prognosticators.

Conclusion: The prognostic impact of pre-PLC was moderate and not prohibiting lung resection. Post-PLC was shown to be a strong independent prognostic factor. Its impact on survival of NSCLC patients was very strong, and therefore should be incorporated in the future TNM classification.

Keywords: PLC, Surgery, prognostic factor, NSCLC

OA07.06 IN EARLY-STAGE LUNG ADENOCARCINOMAS, SURVIVAL BY TUMOR SIZE (T) IS FURTHER STRATIFIED BY TUMOR SPREAD THROUGH AIR SPACES
Takashi Eruchi,1 Koji Kameda,1 Shoahua Lu,1 Matthew Bott,2 Kay See Tan3, David Jones1, William Travis,1 Prasad Adusumilli1
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Background: We investigated whether tumor spread through air spaces (STAS) further stratifies survival beyond tumor size, T-descriptor independent of resection type (lobectomy or limited resection) and surgical margin.

Methods: In patients with pT1a-T2bN0M0 lung adenocarcinomas (LADC, n=1399), tumor size, distance of STAS from the tumor, type of resection, surgical margin were evaluated. The patients with ≤2 cm tumors were divided into STAS(−) (n=561) and STAS(+) (n=307) and their cumulative incidence of recurrence (CIR), and lung cancer-specific death (CID) were compared with patients with larger tumors (2-3 cm, n=299) by use of competing risk analysis.

Results: Of 1399 tumors, 521 (37%) were STAS(−). Compared to STAS(−), recurrence rates were higher with STAS(+) tumors even when the margin is ≥tumor size (Figure 1). In patients with ≤2 cm STAS(+) tumors, CIR and CID are higher than in patients with larger (2-3 cm) tumors (Figure 2). The poor prognostic influence of STAS(+) was evident even when analyzed by the procedure or occurrence pattern (Figure 2 Table). Conclusion: STAS further stratifies survival beyond tumor size, T-descriptor in early-stage (pT1a-2b) lung adenocarcinoma based on the higher prognostic potential for recurrence and lung cancer-specific death independent of the type of resection or margin.

Figure 1. Surgical margin vs. tumor size with recurrence plots
(X-axis, Tumor Size; Y-axis, Surgical margin)

Figure 2. Cumulative incidence of recurrence and lung cancer-specific death
≤2 cm STAS(−) vs. ≥2 cm STAS(+) vs. 2-3 cm STAS(+)

Keywords: surgical margin, sublobar resection, upgrading, T-factor

SESSION OA08: TARGETED THERAPIES IN BRAIN METASTASES
MONDAY, DECEMBER 5, 2016 - 16:00-17:30

OA08.01 EXPLORATION OF THE UNDERLYING MECHANISMS OF LEPTOMENINGEAL METASTASIS IN NSCLC PATIENTS THROUGH NGS OF CEREBROSPINAL FLUID
Yun Fan,1 Min Hu,2 Xuehua Zhu,2 Mengzhao Wang,2 Yanjun Xu1, Xuesong Lv2, Huiyan Xu1, Jingyan Ding1, Xin Ye1, Luo Fang1, Zhiyu Huang1, Lulu Miao1, Lei Gong1, Weimian Mao1, Hongyang Lu1
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Background: Leptomeningeal carcinomatosis (LMC) is a rare but devastating complication of advanced cancer, associated with reduced survival and limited therapeutic options. The role of Next-Generation Sequencing (NGS) of cerebrospinal fluid (CSF) in diagnosis and treatment of LMC is not well established.

Methods: We performed an institutional retrospective analysis of 12 patients with LMC at the National Cancer Center Hospital East, Japan. The patients had CT/MRI scans, cerebrospinal fluid cytology, and CSF NGS performed. A targeted NGS panel targeting tumor exons, fusion transcripts, and non-coding alterations was used.

Results: The median survival from the diagnosis of LMC to death or last follow-up was 6.2 months (range, 1.5-21 months). The median time from the diagnosis of LMC to death was 16.7 months (range, 5.6-40.3 months). All patients had NSCLC, 8 (67%) had adenocarcinoma, 3 (25%) had squamous cell carcinoma, and 1 (8%) had large cell carcinoma. The most common primary sites were the lung (83%), breast (17%), and unknown (17%). The median survival from the diagnosis of NSCLC to the diagnosis of LMC was 12.9 months (range, 2.1-62.5 months). The median overall survival from the diagnosis of NSCLC to death or last follow-up was 14.4 months (range, 0.6-44.7 months).

Conclusion: NGS of CSF is a promising tool for the diagnosis and management of LMC. It can provide valuable information about the genetic landscape of the tumor, which may guide personalized treatment strategies.

Keywords: Leptomeningeal Metastasis, NSCLC, Cerebrospinal Fluid, Next-Generation Sequencing
Background: About 10% of non-small cell lung cancer (NSCLC) patients with EGFR mutations will develop leptomeningeal metastasis (LM) either at initial diagnosis or during treatment. LM is a devastating complication of NSCLC associated with poor prognosis. The median overall survival is 4.5-11 months, with ~60% death due to LM or LM together with systemic lesions. However, the underlying mechanisms of the metastasis process are still poorly understood. Methods: We performed next generation panel sequencing of primary tumor tissue, cerebrospinal fluid (CSF) and matched normal controls from 11 EGFR-mut NSCLC patients with LM. Among them, 2 patients had LM at initial diagnosis, and 8 patients developed LM during their 1st generation EGFR TKI treatment, while such clinical information was missing for 1 patient. Results: The status of EGFR active mutations was the same in the primary tumor and CSF in 7 out of 8 patients who developed LM during TKI treatment. PIK3CA E545K and H1047L, and PTEN R130Q were identified in primary site and/or CSF of 6 patients. Although with small sample size, this ratio is much higher than what was reported in general EGFR L858R or 19Del positive lung adenocarcinoma patient population (~2% from 4 datasets), indicating CSF alterations in PIK3CA pathway may arise with LM risk Interestingly, in 9 of the 11 patients, only 0.9%-7.8% of variants in CSF samples overlapped with those in primary site, suggesting tumor heterogeneity, divergence and clonal evolution during LM development. Moreover, when we cataloged the recurrent CSF-unique somatic genomic alterations existing in ~5 patients, we identified genes involved in DNA repair pathway, cell cycle regulation and epigenetic reprogramming (NPM1, RAD50, MRE11A, POLE, CHEK1, XPC, KMT2B, KMT2C, KMT2D, and ATRX). Conclusion: In summary, our study has shed light on the genomic variations of LM and paved the way for potential therapeutic approaches to this unmet medical need.

OA08.02 PHASE II STUDY OF ERLOTINIB IN ADVANCED NON-SMALL CELL LUNG CANCER PATIENTS WITH LEPTOMENINGEAL METASTASIS (LOG11010)
Keichi Ota 1, Yoshimasa Shiraisi 1, Taishi Harada 1, Daisuke Himeji 2, Takeshi Kitazaki 1, Noriyuki Ebisu 1, Akinobu Hamada 3, Takeshui Yanamaka 1, Kaname Nakao 4, Mitsunori Hayaizama 5, Kenji Nosaki 6
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Background: Leptomeningeal metastases (LM) occur in almost 5% of non-small cell lung cancer (NSCLC) patients (pts) and are associated with a poor prognosis. To date, no prospective study has identified active chemotherapy for LM pts. In retrospective studies, EGFR TKI treatment has been reported to be effective in the treatment of LM. We conducted a multi-center, single-arm phase II trial to evaluate the efficacy of erlotinib in pts with LM. Methods: NSCLC pts with cytologically confirmed LM were eligible and received erlotinib 150mg daily. Overall cytological response rate (ORR, defined as number of pts who achieve complete remission in CSF / number of all pts) was 3.1 months. Time to LM progression (TTP), overall survival (OS) and pharmacokinetics were analyzed. Under the null hypothesis, the regimen would be rejected if confirmed ORR was 5% or less. This study was closed because of low accrual with only 21 of required 32 pts (65 %) accrued. Results: From Dec 2011 to May 2015, 21 pts (17 pts with EGFR mutation) were enrolled. CSFs available for EGFR mutation analysis (N=17) were all EGFR T790M negative. ORR was 30% (95% CI 12.5-54%). Median TTP was 2.3 months. Median OS was 3.1 months. Significantly longer TTP and OS were observed in EGFR-mutant than in EGFR-wild type (P=0.0054 and P=0.0001, respectively). Seven pts survived longer than 12 months. OS of patients with a mutation rate of OS (MOS) was 3.1 3.0 vs 0.7 months. There was no correlation between CSF concentration and clinical efficacy. Conclusion: Erlotinib treatment for LM is active, especially in EGFR-mutant. Our findings suggest that erlotinib could represent a treatment option for LM patients with EGFR mutations.
small-cell lung cancer (NSCLC) patients harboring epidermal growth factor receptor (EGFR) mutation. However, there were few reports about the cerebrospinal fluid (CSF) penetration rate and the efficacy for central nervous system (CNS) metastasis. Therefore, we evaluate the CSF penetration rate and efficacy of AFA in NSCLC patients harboring EGFR mutation with leptomeningeal carcinomatosis (LMC). Methods: Eligibility criteria included performance status (PS) 0-3, aged 20 years or older, pathologically proven NSCLC, harboring EGFR mutation, with LC, adequate organ function, and written informed consent. Patients received AFA (40mg/body every day). We analyzed the blood and CSF level of AFA before administrating AFA on the eighth day. The primary endpoint was the CSF penetration rate. Secondary endpoints included objective response rate (ORR), progression free survival (PFS), overall survival (OS), and safety profile. Results: A total of 11 patients were enrolled. And we could analyze the blood level in 10 patients and the CSF level in 8 patients. Median patient's age was 66 years old. All patients were adenocarcinoma. In EGFR mutation status, 5 patients had exon 19 deletion, 3 had L858R and 3 had minor (exon18) mutation. The patients with PS 2 were 3 patients and PS 3 were 4 patients. Almost all patients received AFA after third-line or more line chemotherapy. The blood level was the Median 88.2 ng/ml (range: 30.4-373), the CSF level was Median 1.4 ng/ml (range: 0.39-2.85) and the CSF penetration rate was Median 0.19% (range: 0.06-0.6%). Hematological toxicity was mild, however we have to take care of severe diarrhea and skin toxicities, especially in patients with poor PS. Conclusion: The median CSF penetration rate (1.65%) of AFA were higher than the penetration rate in previous studies, though the efficacy for the LMC penetration rate was Median 1.65% (range: 0-19.25). The ORR is 27.3%, and two of three patients with exon 18 mutation showed the partial response. Median OS was 3.8 months (95%CI: 1.1-13.1) and median PFS was 2.0 months (95%CI: 0.6-5.8). Hematological toxicity was mild, however we have to take care of severe diarrhea and skin toxicities, especially in patients with poor PS.

Keywords: leptomeningeal carcinomatosis, cerebrospinal fluid penetration rate, EGFR mutation, afitinib

S140

Abstracts

Journal of Thoracic Oncology • Volume 12 Issue S1 January 2017
Background: The eighth edition of lung TNM does not change any N descriptors, but it suggests some potential changes that might be used in the next edition. In fact, N2 would be divided into three groups: pN2a1 (skip lymph-node involvement), pN2a2 (multiple mediastinal involvement) and pN2b (multiple mediastinal involvement). The aim of this study was to verify the value of this classification proposing analysis of our recent surgical experience. Methods: We retrospectively selected all patients treated with lobectomy, bilobectomy or pneumonectomy for T1/T2 N2 NSCLC (VII TNM edition) in the period between 2006 and 2010. We excluded all patients who underwent any kind of extended resection and who had another active tumor at the time of operation. A systematic lymph-node dissection was always carried out according to the IASLC guidelines. All patients were then restaged according to the new IASLC proposal. Overall Survival (OS), Disease Free Interval (DFI) and most important variables were analyzed. Results: Among 248 surgically treated pN2 patients, 108 entered our inclusion criteria. Pathology report showed a majority of T2 tumors (67,6%) and in almost half of cases an adenocarcinoma (50,9%); a mean number of 16,6 (DS 7,8) lymph-node were resected (5,8 (DS 2,9) from the hilum and 10,6 (DS 5,9) from the mediastinum). Among 248 patients, median follow up of 93 months, the median overall survival of the entire cohort was 27 months. pN2a1 had a significant better overall survival compared with the other two groups (p=0.020); conversely no statistically significant difference was found in OS between pN2a2 and pN2b. 1,3 and 5-year survival for pN2a1, pN2a2 and pN2b were 50%, 11% and 17%; 73%, 10% and 18%; 45%, 15% and 14% respectively. Concurrently DFI was significantly better for pN2a1 (p=0.025). Univariate survival analysis age 65 years, more than 4 positive lymphnodes and postoperative complications were statistically significant variables. At the multivariate analysis only the age and the number of positive lymphnodes were independent prognostic factors of a worse survival. Conclusion: Our experience partially validate the new IASLC of N2 staging. Patients with skip lymph-node metastasis (pN2a1) have a statistically significant better prognosis. Concurrently we observed and confirmed the important prognostic value of the number of the involved lymph-node, which should be considered as well in the next editions of the lung cancer staging system. Keywords: pN2 lung cancer, staging system, skip metastasis, NSCLC

OA09.03 RANDOMIZED CONTROLLED STUDY COMPARING ADJUVANT VERSUS NEO-ADJUVANT CHEMOTHERAPY IN RESECTABLE STAGE IIB TO IIIA NSCLC
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Background: Adjuvant chemotherapy is the standard of care for completely resected stage II-IIIa non-small cell lung cancer (NSCLC). A few trials suggest that neoadjuvant chemotherapy is a promising strategy for resectable NSCLC. Indirect comparison meta-analysis of adjuvant versus neoadjuvant therapy showed no difference in survival. This study was conducted to determine the difference of disease-free survival (DFS) between adjuvant chemotherapy and neoadjuvant chemotherapy among patients with resectable NSCLC. Methods: Patients with clinical stage IIB-IIIA NSCLC were eligible. Patients were randomly assigned to 3 cycles adjuvant DC (Docetaxel: 75mg/m2, Carboplatin:AUC=5 on day 1, every 3wk) after completely resection (lobectomy or pneumonectomy with mediastinal lymphnode dissection, or 3 cycles neoadjuvant DC at the same schedule followed by surgery 3-6 wk after chemotherapy. The primary end point was 3 years DFS; secondary end points were 3ys and 5ys Overall Survival(OS) and Safety. Planned sample size is 410. The trial was early closed because slowly accrued. Results: Between March 2006 and May 2011,198 patients from 8 Institute were randomized to neoadjuvant arm (97 cases) or adjuvant arm (101 cases). The median age was 58, male accounted for 80.3%, Adenocarcinoma 48.5%, stage Ib, II a, II b and IIIa were 32.5%, 12.2%, 28.4% and 26.9% respectively. Two arms were balanced. 100% cases received neoadjuvant chemotherapy among patients with resectable NSCLC. Differences of survival between adjuvant and neoadjuvant therapy were not statistically significant. Conclusions: Indirect comparison meta-analysis of adjuvant versus neoadjuvant therapy showed no difference in survival. This study was conducted to determine the difference of disease-free survival (DFS) between adjuvant chemotherapy and neoadjuvant chemotherapy among patients with resectable NSCLC. No unexpected toxicities were seen and 41.2% of patients experienced grade 3-4 neutropenia. In neoadjuvant arm, the ORR was 34% and 12.4% patients experienced grade 3-4 neutropenia. In adjuvant arm, the ORR was 34% and 12.4% patients experienced grade 3-4 neutropenia. In adjuvant arm, the ORR was 34% and 12.4% patients experienced grade 3-4 neutropenia. In adjuvant arm, the ORR was 34% and 12.4% patients experienced grade 3-4 neutropenia. In adjuvant arm, the ORR was 34% and 12.4% patients experienced grade 3-4 neutropenia.
Conclusion: Adjuvant or neo-adjuvant chemotherapy with docetaxel plus carboplatin in resectable clinical stage IB-IIIA NSCLC are feasible and safe. The final results showed no difference in 3y DFS and OS between two arms. Long term survival in Adjuvant arm show the tendency of superior to neoadjuvant arm.

Keywords: ADJUVANT, non-small cell lung cancer, neoadjuvant, chemotherapy

**OA09.05 POSITRON EMISSION TOMOGRAPHY (PET) WITH 18F-FLUOROAZOMYCIN ARABINOSIDE (FAZA) TO ASSESS TUMOR HYPOXIA IN NON-SMALL CELL LUNG CANCER (NSCLC)**

Angela Lin1, Douglass Vines1, Brandon Driscoll2, Lisa Le3, Stephen Breen3, Alexander Sun1

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**Background:** Tumor hypoxia is an adverse prognostic factor in many cancers. Hypoxia tracer 18F-FAZA provides a non-invasive method of hypoxia imaging. This study aims to evaluate the feasibility and potential benefits of using FAZA-PET scans to assess NSCLC tumor hypoxia. Methods: The initial 17 patients of an ongoing study with stage II–III NSCLC have been analyzed prospectively by imaging with FAZA-PET before initiation of a radical course of radiotherapy. The hypoxic volume (HV) was defined as all voxels within the tumor with standard uptake value (SUV) more than 1.2 times the aorta SUVmean. The HV/total tumor volume (T/B) was defined as maximum tumor SUV divided by aorta SUVmean. The hypoxic fraction (HF) was determined by dividing the HV by the entire gross tumor volume. Spearman correlation and Fisher’s test were used to explore potential correlations among several variables. Results: Median primary and nodal FAZA SUVmax were 1.7 (range: 1.0–3.8) and 1.7 (range: 1.0–3.3). Median primary and nodal T/B ratios were 1.4 (range: 1.0–2.5) and 1.3 (range: 1.0–2.2). Median primary and nodal HF were 3.9% (range: 0.0–38.2%) and 0.6% (range: 0.0–50.7%). The median time from diagnostic FDG PET to study FAZA PET scans was 28 days (range: 1–63). Median primary and nodal FDG SUVmax were 13.5 (range: 5.1–32.3) and 8.3 (range: 2.3–15.7). Larger primary tumor volume is correlated with higher FAZA-T/B (p<0.01) and higher HF (p=0.01). Primary tumors with higher T/B also had higher HF (p<0.0001). The same correlations also apply to nodal disease. Nodal FAZA SUVmax is correlated with primary FAZA SUVmax (p=0.0001). When comparing FAZA-PET with FDG-PET, nodal FDG SUVmax is correlated with nodal FAZA T/B (p=0.01) and nodal FAZA HF (p=0.01), which was not observed for primary disease. For each patient, the nodal station with the highest FAZA SUVmax correlates with the highest FDG PET SUVmax (p=0.02). Conclusion: Imaging intra-tumoral hypoxia in NSCLC primary and nodal tumors is feasible and hypoxic tumors achieve with FAZA-PET. Larger tumor volume is correlated with higher T/B and HF in both primary and nodal masses. In the nodal volume only, higher FDG activity is correlated with higher FAZA T/B and higher HF. Ongoing trial accrual and follow-up of our patient cohort will provide more information with regards to the imaging and clinical value of FAZA-PET. This study may eventually lead to using FAZA-PET as a guiding tool to escalate dose to the hypoxic region of the tumor.

Keywords: Hypoxia, FAZA, lung cancer, imaging

**OA09.06 METFORMIN USE DURING CONCURRENT CHEMORADIOThERAPY FOR LOCALLy ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC)**

Krista Wink1, José Belderbos2, Edith Dielemann, Maddalena Rossi3, Coen Rasch4, Ronald Damhuis1, Ruud Houben1, Esther Troost1

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This abstract is under embargo until December 6, 2016 at 07:00 CET.

**OA09.07 INDIVIDUAL ISOXIC RT DOSE ESCALATION BASED ON V20 AND ADVANCED TECHNOLOGIES BEnEFIT STAGE III NSCLC TREATED WITH CCRT**

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**Background:** RTOG 0617 recommended 60Gy as the standard dose for unresectable stage III non-small cell lung cancer (NSCLC) treated with concurrent chemoradiotherapy (CRT) is the conclusion true? The phase I/II trial to determine the feasibility and effects of individual isoxic radiation dose escalation in unresectable stage III NSCLC treated with CRT based on bilateral lung V20 and advanced technologies was studied.

**Methods:** Consecutive patients with unresectable stage III NSCLC were entered in cohorts of eight from March 2006 to May 2009. Patients were assigned to receive concurrent administration of late course accelerated hyperfractionation (LCAHF) intensity modulated radiotherapy (IMRT) and chemotherapy. Isoxic dose escalation was based on V20 and advanced technologies including PET-CT, single photon emission computed tomography (SPECT) and LCAHF IMRT. PET-CT was used to delineate the gross tumor volume. SPECT lung perfusion was applied to define different functional lung regions, which was used to optimize the IMRT plans. Patients with a V20 of 27% as a base level were enrolled into the first cohort. From the second cohort, the V20 further increased to 30%, 33%, 35%, 37% and so on. The criteria for cessation of dose escalation was defined as more than 25% of patients in the cohort experienced dose limiting toxicity (DLT). To test the power of escalation dose, patients with total radiation dose over 66Gy would be assigned to the higher dose group (HD), while the other patients would be assigned to the standard dose (SD). Results: Twenty-nine patients were enrolled. The maximum tolerated value of V20 was 37% in this study. Nineteen patients entered SD group, while twenty-one in HD group. The overall response rate was as high as 80%. Follow-up for all patients ranged from 1 to 112 months with survival patients from 101 to 112 months. The median overall and progression free survivals were 25.0 and 13.0 months, respectively, 1, 3, 5- and 8-year overall survival (OS) rates were 72.5%, 22.5%, 15.0%, and 10.0%, respectively. Patients with stage IIIa achieved a longer median OS than those of stage IIb (31 vs. 21 months, P=0.029). Especially, patients received HD radiotherapy got a significant better OS and local recurrence free survival than those in SD (27.23 vs. 16, 19 months, P=0.053, 0.037) without increasing severe toxicity.

**Conclusion:** The protocol is feasible and effective. In the future, the radiation dose escalation for unresectable stage III NSCLC treated with CRT should be focused on toxicity control and advanced technology application.

Keywords: Individual isoxic dose escalation, Advanced radiotherapy technologies, Non-small-cell lung cancer, concurrent chemoradiotherapy

**SESSION OA01: EGFR MUTATIONS**

**OA10.01 COMPREHENSIVE GENOMIC PROFILING AND PDX MODELING OF EGFR EXON 20 INSERTIONS: EVIDENCE FOR OSIIMERTINIB BASED DUAL EGFR BLOCKADE**

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EGFR exon 20 insertion mutations (EGFRex20ins) comprise a subset of EGFR activating mutations relatively insensitive to 1st and 2nd generation EGFR-TKIs. Comprehensive genomic profiling (CGP) integrated with PDX modeling may identify new EGFR inhibition strategies for EGFRex20ins. Methods: EGFRex20ins and co-occurring genomic alterations were identified by hybrid-capture based CGP performed on 14,483 consecutive FFPE lung cancer specimens to a mean coverage depth of >650X for 236 or 315 cancer-related genes plus 47 intrans from 19 genes frequently rearranged in cancer. An EGFRex20ins(N771_P772)SVDNP/EGFR amplified tumor (24 copies) from this cohort was implanted subcutaneously into the flank of NOD. **Abstracts**

**Journal of Thoracic Oncology • Volume 12 Issue S1 January 2017**
Cg. Prkdc<sup>−/−</sup>Il2rg<sup>−/−</sup>tg<sup>WJ2</sup> (NSG) mice for tumor growth inhibition studies (TGI) with vehicle, erlotinib (50 mg/kg PO daily), osimertinib (25 mg/kg PO daily), and cetuximab (25 mg/kg PO daily) plus cetuximab (10 mg/kg IV, 3x/week) and monitored for 21 days. Results: CCGP identified 263/744,483 cases (1.8%) with EGFRex20ins, which represent 12% (263/2,251) of EGFR activating mutations in this series. 90% (237/263) were NSCLC adenocarcinoma, 9% (23/263) were NSCLC-NOS, and 1% (2/263) were sarcomatoid carcinoma. Over 60 unique EGFRex20ins were identified, most commonly D770, N771/SVDPN (2% and N771, P772-SVDPN (20%), 6% (15/263) harbored EGFR A763_Y764insFQEA, an EGFRex20ins typically sensitive to erlotinib. Among EGFRex20ins cases, EGFR amplification occurred in 5% (57/263). Putative co-occurring driver alterations including EGFR (ex19del and L858R), Her2, MET and KRAS tended to be mutually exclusive, occurring only in 5% (12/263) of cases. The most common co-occurring alterations affected TP53 (56%), CDKN2A (22%), CDKN2B (16%), NXKX2-1 (14%) and RN1 (11%). Average tumor mutation burden was low (mean 4.3 mutations/Mb, range 0-40.3 mutations/Mb). Clinical outcomes to 1st and 2nd generation EGFR-TKIs were obtained for a subset of cases with various EGFRex20ins, and 0/5 patients had responses. However, robust TGI was observed with combination osimertinib and cetuximab in a highly EGFR-amplified PDX model with a conserved EGFRex20ins (N771, P772-SVDPN) not associated with response to earlier generation EGFR-TKI, and was superior to vehicle, erlotinib or cetuximab alone (D21 mean tumor size 70 mm<sup>2</sup> vs. 1000, 800, 225 mm<sup>2</sup> respectively; p values all <0.001).

Conclusion: Diverse EGFRex20ins were detected in 12% of EGFR-mut NSCLC. Available clinical outcomes data demonstrated lack of response to 1<sup>st</sup> and 2<sup>nd</sup> generation EGFR-TKIs. Identification of co-occurring EGFR-amplification in 22% of cases led to testing of a dual EGFR blockade strategy with an EGFR monoclonal antibody and osimertinib, which demonstrated exceptional tumor growth inhibition in an EGFRex20ins PDX minimally responsive to erlotinib. These findings can rapidly be translated into an ongoing clinical trial of osimertinib and nectumumab.

Keywords: PDX, EGFR Exon 20 Insertion, Genomic Profiling

OA10: EGFR MUTATIONS
TUESDAY, DECEMBER 6, 2016 - 11:00-12:30

OA10.02 ASSOCIATION OF VARIATIONS IN HLA-CLASS II AND OTHER LOCI WITH SUSCEPTIBILITY TO EGFR-MUTATED LUNG ADENOCARCINOMA


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Background: Lung adenocarcinoma (LADC) driven by somatic EGFR mutations is more prevalent in East Asians (30-50%) than in European/Americans (10-25%). Understanding the genetic factors underlying such lung LADC is required to elucidate disease etiology and to identify effective methods of prevention. Methods: We investigate genetic factors underlying the risk of this disease by conducting a genome-wide association study, followed by two validation studies, in 3,173 Japanese patients with EGFR-mutation-positive lung adenocarcinomas. Results: Four loci, 5p15.33 (FERT), 6p21.3 (BTLN2, HLA-class II), 3q28 (TP53) and 17q24.2 (BPTF), previously shown to be strongly associated with overall lung adenocarcinoma risk in East Asians, were re-discovered as loci associated with a higher susceptibility to EGFR-mutation-positive lung adenocarcinoma. In addition, two additional loci, HLA-class II at 6p21.32 and 6p21.11 (FOXPA) were newly identified as loci associated with EGFR mutation-positive lung adenocarcinoma (Shiraiishi et al., Nature Communications, 2016, in press). Conclusion: This study indicates that multiple genetic factors, including an immunologic one, underlie the risk of lung adenocarcinomas with EGFR mutations.

Keywords: HLA class II, EGFR, lung adenocarcinoma, SNP
Results: Pathways mediating EGFR mutations are: i) ERK1/2 via Ras and MEK1/2 ii) AKT via PI3K and iii) STAT3 via JAK (Figure). By Western blot analysis, phosphorylation of Tyr705 on STAT3 was noted after 2 hours of gefitinib or osimertinib treatment in PC9 and H1975 EGFR mutant cells. Unexpectedly, YAP1 phosphorylation on Tyr357 and Notch activation was detected. Co-targeting STAT3 and Src with gefitinib or osimertinib ablates activation of STAT3 and YAP1-NOTCH3 signaling pathways (Figure). In vitro and in vivo, the combinatorial therapy of gefitinib or osimertinib plus TPCA-1 (a dual inhibitor of I KK and STAT3) plus saracatinib (a SFK inhibitor) leads to significant tumor shrinkage in PC9 and H1975 cells.

In tumor samples of 64 EGFR mutant NSCLC patients treated with gefitinib, the median progression free survival (PFS) was significantly shorter in those with high levels of HES1, ALDH1A1, ALDH1A3, Bmi1, AXIN1, CDCP1, SHP2 and ILK (Figure). However, the mRNA levels of STAT3 and YAP1 stand out in the prediction of shorter PFS with a hazard ratio of 3.02 and 2.57, respectively (P<0.001).

Conclusion: For the first time ever, we reported gefitinib induced activation of theYAP1-NOTCH signaling pathway, in addition to activation of STAT3, in EGFR mutant cells. Secondly, co-targeting STAT3 and Src, together with EGFR, causes significant tumor growth inhibition, in comparison with gefitinib or osimertinib single therapy.

Keywords: YAP-NOTCH, STAT3 signaling, EGFR mutant lung cancer, osimertinib

OA10: EGFR MUTATIONS
TUESDAY, DECEMBER 6, 2016 - 11:00-12:30

OA10.05 EGFR GENE MUTATIONS AFFECT TUMOR-INFILTRATING Stromal CELL COMPONENTS IN EARLY-Stage LUNG ADENOCARCINOMA
Toshiyuki Shima1, Takao Shigenobu1, Masayuki Shimoda1, Takashi Ohtsuka1, Hisao Asamura1, Yae Kanai2
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Background: Tumors are complex structures consisting of cancer cells surrounded by a tumor stroma that is now recognized to be critical for cancer progression. Although epidermal growth factor receptor (EGFR) mutations are frequently observed in non-small cell lung carcinoma, it remains poorly understood whether EGFR mutations in cancer cells affect the tumor stroma.

In this study, we studied the status of EGFR mutations in early-stage lung adenocarcinoma and analyzed the relations of EGFR mutations to tumor-infiltrating stromal cell components. Methods: A total of 152 consecutive patients with clinical stage IA lung adenocarcinoma who underwent complete resection in Keio University Hospital between 2010 and 2014 were studied. Genomic DNA was isolated from formalin-fixed, paraffin-embedded tumor sections and mutational analyses of EGFR gene exons 19, 20 and 21 were performed by a polymerase chain reaction-based method. Paraffin sections were also subjected to immunohistochemistry for CD3, FOXP3, CD163 or CD204. Numbers of CD3+, FOXP3+, CD163- or CD204-immunostained cells were counted by observing 5 different fields at x200 magnification. Results: EGFR mutations were detected in 71 (47%) of the 152 patients with clinical stage IA lung adenocarcinoma and were found more frequently in women and non-smokers. These contained 38 patients with missense mutations in exon 21 (L858R) and 30 patients with deletions in exon 19. By immunohistochemistry, the number of stromal macrophages positive for CD163 or CD204, markers for tumor-associated macrophages (TAMs), was significantly decreased within tumors with EGFR mutations compared to within those with wild-type EGFR, whereas the number of CD3+ T cells or FOXP3+ regulatory T cells was comparable between these groups. Both tumors with missense mutations in exon 21 and deletions in exon 19 had a similar trend toward decreased TAMs in the tumor stroma. Conclusion: Our data suggest that EGFR mutations in early-stage lung adenocarcinoma are associated with decreased TAMs in the tumor stroma. EGFR mutation status might act on not only cancer cell behavior but tumor microenvironment.

Keywords: EGFR gene mutations, tumor-infiltrating stromal cell, early-stage lung adenocarcinoma

OA10.06 CHARACTERISTICS AND OUTCOMES OF PATIENTS WITH LUNG CANCER HARBORING MULTIPLE MOLECULAR ALTERATIONS (BIOMARKER IFCT STUDY)
Nicolas Guibert1, Fabrice Barlesi2, Renaud Descourt3, Hervé Léna4, Benjamin Besse5, Michèle Beau-Faller6, Jean Mosser7, Eric Pichon7, Jean-Philippe Merlio7, L’Houcine Ouafik8, François Guichard9, Bénédicte Mastroianni9, Lionel Moreau10, Annie Wdowik11, Jean-Christophe Sabourin12, Antoinette Lemoine13, Pascale Missy14, Alexandra Langlais15, Denis Moro-Sibilot16, Julien Mazieres17
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targeting the dominant oncogene remain generally active in this setting. Should be reconsidered. Double mutations do not significantly decrease OS between single and multiple alterations whatever the type of mutations.

Results: We identified 162 (68%) patients with double genetic alterations and 3 (1.3%) patients with triple alterations. Multiple mutations involved preferentially KRAS (67.3%), PIK3 (53.3%) and EGFR (42.4%). Patients with multiple mutations were male (56.4%) with a median age of 68.7 and essentially adenocarcinoma (83.6%). More never-smokers were observed in comparison with patients with single alterations (34.7% vs. 25.8%, p<0.001). OS, DFS and PFS were not significantly different between single and multiple alterations whatever the type of mutations. Patients with EGFR/KRAS and EGFR/PIK3 mutated tumors had worse PFS after biomarker analysis than patients with EGFR single mutation (71.7 and 71.0 months vs. 51.7 and 55.4 months respectively, p<0.01). OS, DFS and PFS were not significantly different between patients harboring ALK rearrangement had little impact on OS (17.7 months vs. 20.3 months, p=0.57) or PFS (10.3 months vs. 12.1 months, p=0.93). Patients harboring KRAS mutations with another alteration had similar OS (13.4 vs. 11.2 months, p=0.28), PFS (6.4 months vs. 7.2 months, p=0.42) and ORR (0.5 vs. 0.6 respectively, p=0.42). Conclusions: Multiple mutations in patients harboring KRAS mutations had worse OS and PFS. Conclusion: With 50% of OS and PFS patients harboring KRAS mutations, the dogma of mutually exclusive mutations should be reconsidered. Double mutations do not significantly decrease OS but alter PFS under first line treatment for EGFR mutated patients. Therapies targeting the dominant oncogene remain generally active in this setting.

Keywords: lung cancer, targeted therapy, mutation, prognosis

**SESSION OA01: ANGIogenesis in ADVANCED LUNG CANCER**

**TUESDAY, DECEMBER 6, 2016 - 11:00-12:30**

**OA01.01 PROLONGED OS OF PATIENTS EXPOSED TO WEEKLY PACLITAXEL AND BEVACIZUMAB: IMPACT OF THE CROSS-OVER IN THE IFCt-1103 ULTIMATE STUDY**

Alexis Cortot1, Clarisse Audigier Valette1, Olivier Molinier1, Sylvestre Le Moulec1, Fabrice Barlesi2, Gérard Zalcman1, Patrick Dumont3, Damien Pouessel1, Claire Poulet1, Sandrine Hiret4, Pierre Jean Souquet1, Adrien Diamier5, Patrick-Aldo Renaut6, Alexandra Langlais7, Marie-Paule Leblanc8,9, Brian2, Luis Raez2, Lilibeth Castillero2, Clarisse Audigier Valette1, Olivier Molinier1, Sylvestre Le Moulec1, Fabrice Barlesi2, Gérard Zalcman1, Patrick Dumont3, Damien Pouessel1, Claire Poulet1, Sandrine Hiret4, Pierre Jean Souquet1, Adrien Diamier5, Patrick-Aldo Renaut6, Alexandra Langlais7, Marie-Paule Leblanc8,9, Brian2, Luis Raez2, Lilibeth Castillero2.

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**Background:** Overall survival (OS) is considered as the gold standard for evaluating efficacy of antineoplastic treatments, including chemotherapy and targeted therapies. In randomized trials, allowing patients to cross-over to the other arm usually prevents demonstration of a survival benefit. However, it may provide important information with clinical relevance.

**Methods:** The phase III IFCt-1503 ULTIMATE study compared weekly paclitaxel and bevacizumab (WPB) vs. docetaxel (DOC) as second- or third-line therapy in non-squamous NSCLC. At progression, patients were allowed to cross over to the other arm. Date of progression was collected for patients who crossed over to the other arm and for those who did not cross over but received a post-discontinuation treatment within 60 days following progression. Post-discontinuation progression-free survival (PFS2) and overall survival (OS2) were calculated from day 1 of post-discontinuation treatment. Results: The study met its primary endpoint, PFS, which was significantly improved in the WPB arm (median 4.5 vs. 3.9 months, hazard ratio (HR) 0.62, p=0.006). No overall survival was observed (median 9.9 vs. 11.4 months, HR 1.18, p=0.4). Out of patients treated with DOC (n=55), those who crossed over to WPB (n=28, 28.2%) had a median PFS2 of 4.9 mo [3.1-6.2] and a median OS2 of 12.5 mo (7.0-NR), whereas those who did not cross over but received a post-discontinuation treatment (n=13, 23.7%) had a median PFS2 of 1.7 mo [1.1-2.2] and a median OS2 of 4.1 mo [2.1-5.9]. Out of patients treated with WPB (n=111), median PFS2 was 1.3 mo [1.2-2.2] for those who crossed over to DOC (n=9, 8.3%) and median PFS2 and OS2 were 1.9 mo [1.7-2.6] and 5.0 mo [3.4-9.0] for those who did not cross over but received a post-discontinuation treatment (n=57, 52.3%). Conclusion: Allowing patients to cross over to the other arm demonstrated benefit of WPB following progression on docetaxel and explains the absence of OS benefit.

**Keywords:** paclitaxel, Second-line, non-small cell lung cancer (NSCLC), bevacizumab

**OA01.07 REPORT ON LIQUID BIOSPSIES FROM ADVANCED LUNG ADENOCARCINOMA PATIENTS AND CORRELATION WITH THEIR TUMOR BIOPSY PROFILES**

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1Department of Oncology, Lynn Cancer Institute/Florida Atlantic University, Boca Raton/Fl/United States of America, 2Florida International University, Memorial Cancer Institute, Pembroke Pines/Fl/United States of America, 3Human Physiology, University of Panama, Panama/Panama.

**Background:** Liquid biopsy (LBx) has emerged as an alternative tool for the management of advanced lung cancer patients (pts) identifying driver mutations, and hence, improving personalized medicine. There are still controversial issues such as standardization, validation of different technologies, concordance with tissue molecular profile results (TMPR), and others. LBx can detect non-invasive, bypass tumor heterogeneity, an opportunity for serial measurements to evaluate response or early recurrence, and others. Methods: Guardian 360 was analyzed in 100 consecutive stage IV or recurrent lung adenocarcinoma (adeno) pts. Guardian 360 is a panel of 70 genes including single nucleotide variations, amplifications, translocations, and short insertions/duplications/deletions in exons 19 and 20 of the EGFR, and others. Cell-free DNA (cfDNA) is extracted from plasma and genomic alterations are analyzed by massively parallel sequencing of amplified target genes. TMPRs from each subject was obtained or recovered for comparison with their LBx counterparts. TMPRs from this cohort was developed in different CLIA laboratories.

**Results:** 69 pts were female median age of 67 (range 49-79) and at least 1 genomic alteration by LRx (range, 1-10). Most common abnormalities found in LRx were: TP53 (37 pts), EGFR (35 pts), NFI (20 pts), KRAS (12 pts), MET (14 pts). From this 84 pts with + LBx results, 67 pts (80%) had TMPRs for comparison. Main reason for lack of TMPRs: insufficient tumor (19/100, 19%). From comparison between the 2 modalities, we considered all pts with available results in both tests; hence, 81 pts were used to compare tumor biopsy (TBx) vs. LRx. 37 pts out of 81 (46%) had at least 1 similar genomic abnormality found in both TBx and LRx, respectively. Most of the concordance was in EGFR alterations (19/26, 78%). LBx caught 16 additional EGFR genomic aberrations not being identified by TBx. A total of 35 EGFR genomics aberrations were identified in LBx, 16/35 EGFR mutations found in LRx were actionable and 5 of these 16 actionable EGFR mutant cases were only found in LBx not in TBx. Conclusion: LBx offers an alternative to identify genomic alterations. Still, insufficient tumor is the major reason for lacking of TMPRs. EGFR mutations are the most common actionable mutations found in LBx; also, it has a high correlation with TBx (68%). LBx identified more gene abnormalities than TBx, and in some cases, the actionable EGFR mutations were found only in LBx sample.

**Keywords:** molecular profile, Driver Mutations, lung adenocarcinoma, liquid biopsy.
Abstracts

**OAT1: ANGIOGENESIS IN ADVANCED LUNG CANCER**
TUESDAY, DECEMBER 6, 2016 - 11:00-12:30

**OAT1.02 RANDOMIZED PHASE 1B/3 STUDY OF ERLOTINIB PLUS RAMUCIRUMBIB IN FIRST-LINE EGFR MUT + STAGE IV NSCLC: PHASE 1B SAFETY RESULTS**

Kazuhiko Nakagawa, Luis Paz-Ares, Santiago Ponce, Jesus Corral, Oscar Vidal, Ernest Nadal, Katsuaki Kuira, Jingyi Liu, Shuang He, Joseph Treat, Rita Dalal, Pablo Lee, Martin Reck

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**Background:** Ramucirumab, an antiangiogenic IgG1 VEGFR2-targeted monoclonal antibody, and erlotinib, an EGFR tyrosine kinase inhibitor, are both active in advanced NSCLC. This global phase 1b/3 study (NCT02411448) will assess safety, tolerability and efficacy of the combination of erlotinib in patients with EGFR mutation-positive stage IV NSCLC. Here we review phase 1b safety results. **Methods:** Eligible patients with EG09 P0.1, achieving EGFR mutation, and previously untreated stage IV NSCLC received ramucirumab 10 mg/kg intravenously on day 1 of repeating 14-day (3 cycles) and erlotinib 150 mg orally daily. Treatment continued until disease progression or unacceptable toxicity. The primary objective of part A was to assess the safety and tolerability, in terms of dose limiting toxicities (DLT), of adding the recommended dose of ramucirumab for phase 3 (part B) to standard dose erlotinib. Data were analyzed separately for Japan (JP) (cohort 1) and US/EU (cohort 2). The DLT assessment occurred during the first 2 cycles (approximately 28 days).

**Results:** As of Dec 16th, 2015, 14 patients were in phase A of part 1b of this trial and 12 DLT were evaluated (6 JP; 6 US/EU). Overall, 6 grade (G) 3 treatment-emergent adverse events (TEAE) were noted, with at least one TEAE in 5 patients; no serious adverse events or G 4-5 TEAEs occurred. In the JP cohort the median age was 73 (64-79), 57% had EG09 P0.1 and 29% had a history of smoking. Four patients (57%) experienced a G 3 TEAE, of which one was a DLT (elevation of alanine aminotransferase while the others (hypertension, dermatitis acniform, and diarrhea) were not DLTs. In the US/EU cohort the median age was 71 (31-83), 86% had EG09 P0.1, and no patients had a history of smoking. One patient experienced G 3 TEAE of rash; no DLTs were observed in this cohort. **Conclusion:** Enrollment on the phase 1b portion of this trial is complete and the safety results were consistent with previously published results from phase 1a. No unexpected toxicities were identified. Phase 3 enrolment has been initiated.

Keywords: Erlotinib, EGFR, VEGF, ramucirumab

**OAT1.03 A RANDOMIZED, MULTI-CENTER, DOUBLE-BLIND PHASE II STUDY OF FRUQUINTINIB IN PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER**

Shun Lu, Jianhua Chang, Xiaoqing Liu, Jianhua Shi, You Lu, Wei Li, Jinji Yang, Jianying Zhou, Jie Wang, Lei Yang, Zhiiwei Chen, Xiongdang Zhou, Zhe Liu, Ye Hua, Weiguo Su

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**Background:** ramucirumab, an antiangiogenic IgG1 VEGFR2-targeted monoclonal antibody, and erlotinib, an EGFR tyrosine kinase inhibitor, are both active in advanced NSCLC. This global phase 1b/3 study (NCT02411448) will assess safety, tolerability and efficacy of the combination of ramucirumab in previously untreated patients with EGFR mutation-positive stage IV NSCLC. Here we review phase 1b safety results. **Methods:** Eligible patients with EG09 P0.1, achieving EGFR mutation, and previously untreated stage IV NSCLC received ramucirumab 10 mg/kg intravenously on day 1 of repeating 14-day (3 cycles) and erlotinib 150 mg orally daily. Treatment continued until disease progression or unacceptable toxicity. The primary objective of part A was to assess the safety and tolerability, in terms of dose limiting toxicities (DLT), of adding the recommended dose of ramucirumab for phase 3 (part B) to standard dose erlotinib. Data were analyzed separately for Japan (JP) (cohort 1) and US/EU (cohort 2). The DLT assessment occurred during the first 2 cycles (approximately 28 days).

**Results:** As of Dec 16th, 2015, 14 patients were in phase A of part 1b of this trial and 12 DLT were evaluated (6 JP; 6 US/EU). Overall, 6 grade (G) 3 treatment-emergent adverse events (TEAE) were noted, with at least one TEAE in 5 patients; no serious adverse events or G 4-5 TEAEs occurred. In the JP cohort the median age was 73 (64-79), 57% had EG09 P0.1 and 29% had a history of smoking. Four patients (57%) experienced a G 3 TEAE, of which one was a DLT (elevation of alanine aminotransferase while the others (hypertension, dermatitis acniform, and diarrhea) were not DLTs. In the US/EU cohort the median age was 71 (31-83), 86% had EG09 P0.1, and no patients had a history of smoking. One patient experienced G 3 TEAE of rash; no DLTs were observed in this cohort. **Conclusion:** Enrollment on the phase 1b portion of this trial is complete and the safety results were consistent with previously published results from phase 1a. No unexpected toxicities were identified. Phase 3 enrolment has been initiated.

Keywords: Erlotinib, EGFR, VEGF, ramucirumab

**OAT1: ANGIOGENESIS IN ADVANCED LUNG CANCER**
TUESDAY, DECEMBER 6, 2016 - 11:00-12:30

**OAT1.05 A PHASE 2 STUDY OF CAPOZABANTINIB FOR PATIENTS WITH ADVANCED RET-REARRANGED LUNG CANCERS**

Alexander Drilon, Romel Somwar, Roger Smith, Lukas Delasos, Melanie Albano, Martine van Voorthuyzen, Lu Wang, Natasha Rekhtman, Andy Ni, Andrew Plodkowski, Michelle Ginsberg, Gregory Reilly, Charles Rudin, Marc Ladanyi, Mark Kris

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**Background:** RET rearrangements are actionable drivers found in 1-2% of non-small cell lung cancers. We previously reported the efficacy and safety of the multitkinae RET inhibitor cabozantinib in 16 patients with RET-rearranged lung cancers in the first stage of our Simon two-stage phase 2 clinical trial (overall response rate 38%; Drilon, ASCO 2015). This study has since completed accrual of both stages, now with 26 patients treated with cabozantinib. **Methods:** This was an open-label, single center, phase 2 trial (NCT01639508). Eligibility criteria: stage IV pathologically-confirmed lung cancers, presence of a RET rearrangement, KPS >70, and measurable disease. RET rearrangements were detected by FISH or next-generation sequencing. Cabozantinib was administered in tablet form at 60 mg daily until progression of disease or unacceptable toxicity. The primary objective was to determine the overall response rate (ORR, RECIST v1.1). Secondary objectives included determining progression-free survival (PFS), overall survival (OS), and toxicity. 5 responses in 25 response-evaluable patients were required to meet the primary endpoint (Simon two-stage minimax design: H0 10% vs H1 30% ORR). All patients who received at least one dose of cabozantinib were evaluable for toxicity. **Results:** 26 patients with RET-rearranged advanced adenocarcinomas were treated with cabozantinib. KIF5B-RET was the predominant fusion type identified in 16 (62%) patients. The median number of prior chemotherapy lines was 1 (0-5). One patient who discontinued therapy in cycle 1 and did not undergo a response assessment was not response-evaluable as per protocol. This study met its primary endpoint. **Conclusion:** 26 patients with RET-rearranged cancer were treated. Cabozantinib was an active agent in patients with RET-rearranged lung cancers.
Background: There is growing evidence that tumor-associated fibroblasts (TAFs) play a major role in critical steps of tumor progression in solid tumors including NSCLC. However, the role of TAFs in regulating the response to targeted therapies is poorly understood. One such targeted therapy is nintedanib (NTD), a multi-kinase inhibitor of VEGF, FGF and PDGF receptors that has been recently approved to treat advanced lung adenocarcinoma (AD) patients. Although the anti-angiogenic effects of NTD in lung cancer have been associated with its antiangiogenic functions, NTD has also been shown to exhibit anti-fibrotic effects in patients with idiopathic pulmonary fibrosis. Since lung fibrosis is largely driven by activated fibroblasts/myofibroblasts, it is conceivable that NTD anti-angiogenic effects may be additionally driven through its direct action on lung TAFs. The main goal of this study was to analyze the latter hypothesis.

Methods: Patient derived lung TAFs from ADC and SCC patients as well as adherent cultured fibroblasts from non-malignant pulmonary tissue were exposed to increasing concentrations of NTD and analyzed for growth and activation upon stimulation with growth factors and TGF-β, respectively. Activation markers included alpha-smooth muscle actin and collagen-I.

Results: We found that NTD exhibited a dual inhibitory role in TAFs in terms of growth and TGF-β1-induced activation in a subtype-specific fashion. Specifically, NTD-mediated growth inhibition was larger in SCA-TAFs than in ADC-TAFs, which correlated with the larger Erk signaling previously reported by our group in SCC-TAFs in the absence of mitogenic stimuli. Conversely, inhibition by NTD of TGF-β1-mediated activation was larger in ADC-TAFs than SCA-TAFs. Likewise, NTD inhibited the growth and invasive advantages of ADC cancer cells in vitro elicited by the conditioned medium of ADC-TAFs treated with TGF-β1 compared to those advantages elicited in the absence of NTD. These results reveal for the first time that the pro-tumorigenic effects of ADC-TAFs in vitro, a predominant signature of NTD, were sensitized by the presence of NTD. Consequences of NTD in different treatment groups and time points by flow cytometry and immunohistochemistry.

Conclusion: NTD significantly inhibited tumor cell growth and invasion in vitro. The antifibrotic effects of NTD may be due to the direct inhibition of growth and activation of TAFs in ADC, leading to a reduction in the TILs density and microvessel density, thus providing novel mechanic insights on the subtype-specific therapeutic effects of NTD in NSCLC.

Keywords: nintedanib, TGF-β, tumor microenvironment, cancer associated fibroblasts

OA11.06 ROLE OF FIBROBLASTS IN THE SUBTYPE-SPECIFIC THERAPEUTIC EFFECTS OF NINTEDANIB IN NON-SMALL CELL LUNG CANCER (NSCLC)

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Dep. of Biomedicine, Facultad de Medicina, Universitat de Barcelona, Barcelona/Spain, 2Boehringer Ingelheim RCV GmbH & Co KG, Vienna/Austria, 3Hospital Clinic Barcelona, Barcelona/Spain

Background: NSCLC is a common malignancy whose incidence is on the rise. Treatments are generally aimed at eradicating tumor cells, but the tumor microenvironment is considered an important contributor to tumor progression. Fibroblasts, a major cell type of the tumor microenvironment, have been shown to interact with tumor cells. The role of fibroblasts in the therapeutic effects of nintedanib (NTD), a multi-kinase inhibitor of VEGF, FGF and PDGF receptors, is not yet fully elucidated.

Methods: We evaluated the antitumor effects of anti-VEGFR2 agent (apatinib) in monotherapy or in combination with anti-PD-1 monoclonal antibody in a murine lung cancer model using Lewis lung cancer cells (LLCs). The changes of immune components in tumor and spleen were dynamically tested in different treatment groups and time points by flow cytometry and immunohistochemistry. Results: The results showed that VEGF/VEGFR2 blockade could retard tumor growth and inhibit tumor neovascularization via eradicating Foxp3+ regulatory T cells (Tregs) and myeloid derived suppressive cells (MDSCs) and reducing the density of microvessels in the tumor. On the third week of apatinib monotherapy, the number of Foxp3+ Tregs and MDSCs had increased again. Although VEGF/VEGFR2 blockade induced more tumor infiltrating lymphocytes (TILs), especially CD8+ T cells, infiltrating into the tumor mass than control group (P < 0.01), the expression of PD-1 and PD-L1 was also significantly upregulated than that control group (P < 0.01). Compared to apatinib monotherapy, combining treatment demonstrated that anti-VEGFR2 plus anti-PD-1 therapy could significantly inhibit tumor growth (P < 0.01) by persistently eliminating Foxp3+ Tregs and MDSCs. Furthermore, combining anti-VEGFR2 and anti-PD-1 therapy could not only dramatically increase TILs infiltration, especially CD8+ T cells, but also significantly reduce the expression of PD-1 and PD-L1.

Conclusion: Simultaneous blockade of VEGF/VEGFR2 and PD-1/PD-L1 pathways induced a synergistic anti-tumor effect in vivo, possibly through eliminating immunosuppressive components including Tregs and MDSCs and enhance antitumor immune response.

Keywords: programmed death ligand-1, lung cancer, Immunotherapy, angiogenesis

OA12: SBRT AND OTHER ISSUES IN EARLY STAGE NSCLC

TUESDAY, DECEMBER 6, 2016 - 11:00-12:30

OA12.01 PHASE II RANDOMIZED STUDY OF 2 SBRT REGIMENS FOR MEDICALLY INOPERABLE PATIENTS WITH NODE NEGATIVE PERIPHERAL NSCLC

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Background: This phase II, multi-institutional (Roswell Park Cancer Institute, Cleveland Clinic, and Upstate Medical Center) randomized study was conducted to compare incidence of RT0G grade 3 or higher adverse events (AEs) associated with 2 different, established SBRT regimens for NSCLC.

Methods: Patients with documented baseline medical conditions precluding lobectomy and biopsy-proven peripheral (greater than 2 cm from the central bronchial tree) T1/T2, NO (clinically node negative by PET), MO tumors were eligible. Patients were randomized to receive either 30 Gy in one fraction (arm 1) or 60 Gy in 3 fractions (arm 2) over at least 8 days. Heterogeneity corrections were not used. Randomization was stratified by treatment center and Karnofsky performance status (100, 90, 80 and below). The study was designed to detect whether psAEs rate >1% at a 5% significance level (1-sided) and 8% power. Secondary endpoints included: local control, greater than 1 year toxicity, overall survival (OS) and progression-free survival (PFS).

Results: The study opened in September 2008, was suspended between April 2010 to June 2010 as well as October 2010 to April 2011 while RT0G 0915 was open, and closed on April 15, 2015 after accruing a total of 98 patients. All patients received planned SBRT treatment. Median follow-up was 27 months. In follow-up, 10 patients were lost to follow-up; 1 was in arm 1 and 9 in arm 2. Baseline patient and tumor characteristics were balanced between both arms. On arm 1, 13 (27%) patients and 16 (33%) patients on arm 2 experienced RT0G grade 3 AEs, there were no grade 4 AEs. Thoracic grade 3 AEs were experienced by 8 (16%) patients on arm 1 and 6 (12%) patients on arm 2. There were no statistically significant differences in OS or PFS survival, logrank P = 0.44 and 0.99 respectively. OS at 2 years was 71% (95% CI, 55-82%) for arm 1 and 61% (95% CI, 44-78%) for arm 2. PFS at 1 year was 63% (95% CI, 46-75%) for arm 1 and 51% (95% CI, 34-65%) for arm 2.

Conclusion: This randomized phase II study demonstrated that 30 Gy in one fraction was equivalent to 60 Gy in three fractions in terms of toxicity, progression free survival and overall survival. Acknowledgment: Supported by Roswell Park Alliance Foundation grant
Abstracts

OA12: SRTB AND OTHER ISSUES IN EARLY STAGE NSCLC
TUESDAY, DECEMBER 6, 2016 - 11:00-12:30

OA12.02 EXCELLENT SURVIVAL ACHIEVED BY STEREOTACTIC BODY RADIOTHERAPY FOR MEDICALLY OPERABLE AND YOUNG (<75 YEARS) PATIENTS WITH STAGE I LUNG CANCER
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Background: Stereotactic body radiotherapy (SBRT) has been sometimes used as a curative treatment for both of medically operable patients with stage I non-small cell lung cancer (NSCLC). However, most of these patients are comparatively high-aged and not similar to the patients cohort generally operated with surgery. So, the purpose of this study was to collect results of SBRT for operable and young (70 years old or younger) patients with stage I NSCLC from multiple Japanese institutions. Methods: We organized a multi-institutional SBRT study group in Japanese Radiological Society (JRS-SBRTSG) and conducted a study for SBRT for stage I non-small cell lung cancer (NSCLC). This is a retrospective analysis to review 252 patients (male 168, female 84) who were medically operable and aged 70 years old or younger (range, 40-74; median, 67 years) with stage I (IA, IB) NSCLC treated with curative intent by SBRT in 20 institutions of JRS-SBRTSG. Histology was proven in 177 patients (adenocarcinoma 121, squamous cell carcinoma 41, others 15), and the others were diagnosed clinically. Median tumor size was 22mm (range, 7-58mm). A total dose of 40-60 Gy was prescribed in 4-10fractions. Median calculated biological effective dose (BED) was 107.6 Gy (range, 75-134 Gy) based on alpha/beta = 10Gy). Results: The median follow-up period for all patients was 37 months. Overall survival rate (OS) at three and five year was 83.3% and 76.6%, respectively. Radiation pneumonitis of grade 3 or more was noted in 0.8% of the total patients. In the total patients, local control rate (LC) at three year was 89.5%, and LC was significantly better in the subgroup of adenocarcinoma than that of squamous cell carcinoma. According to univariate analysis, female, adenocarcinoma, no emphysema, and no pulmonary interstitial change were better prognostic factors for OS. According to multivariate analysis, pulmonary interstitial change was only a worse survival factor for OS. OS at three and five year in the subgroup of patients without pulmonary interstitial change was 89.7% and 84.0%, respectively. Conclusion: The outcomes of SBRT for the medically operable and young patients with stage I NSCLC in the Japanese large database of practice level was excellent and the overall survival rate would be comparable to that of surgery. The results will support a rationale of applying SBRT for younger and operable patients with operable stage I NSCLC.

Keywords: stereotactic body radiotherapy, stage I, non-small cell lung cancer, operable

OA12: SRTB AND OTHER ISSUES IN EARLY STAGE NSCLC
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OA12.05 NONINVASIVE CT-BASED IMAGE BIOPSY SYSTEM (IBIOPSY) FOR EARLY STAGE LUNG ADENOCARCINOMA
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Background: CT screening programs frequently detect early stage lung adenocarcinoma. Recent studies show that distinct subtypes of lung adenocarcinoma are associated with different prognosis and suggest that treatment should be tailored to histological subtypes as identified in the new WHO Lung Tumor Classification. To develop this personalized approach, it is important to have reliable tools to diagnose tumors before treatment, preferably non-invasively through image analysis. We have developed a CT-image analysis system (IBiopsy) that uses computerized deep learning and artificial intelligence. To validate the accuracy of a noninvasive CT-based image biopsy system (IBiopsy) in differentiating early stage lung adenocarcinoma subtypes of atypical adenomatous hyperplasia (AAH), adenocarcinoma in situ (AIS), minimally invasive adenocarcinoma (MIA) and invasive adenocarcinoma (IAC). Methods: We retrospectively identified 365 eligible patients from Zhongshan Hospital Fudan University, diagnosed with AAH, AIS, MIA or IAC by diagnosis. The last high definition CT scan prior to the surgery of the lesion was analyzed using the ibiopsy system, blinded to pathological result. Based on a pulmonary nodule image feature set (PNIFS) in combination with classified pattern models, such as R-SVM, all the pulmonary nodules were classified into four groups. For diagnosis efficacy, area under the curve (AUC) of Precision-Recall score (PRS), receiver operating characteristic (ROC) of a classification model were calculated in each group. Results: 365 patients were included in the analysis. The classification recognition rate of the PRIFS was 80.03%. The average value of PRS is 0.92, the mean of ROC is 0.95, and it is more than 0.80 for the cross validation value. Conclusion: IBiopsy system allows the non-invasive imaged based stratification of pulmonary adenocarcinoma nodules into four groups, from AAH to IAC. Our result suggest that IBiopsy system could ultimate facilitate the diagnosis and precision management of pulmonary nodules.

Keywords: CT scan, lung adenocarcinoma, pulmonary nodule, image analysis

OA12: SRTB AND OTHER ISSUES IN EARLY STAGE NSCLC
TUESDAY, DECEMBER 6, 2016 - 11:00-12:30

OA12.06 A RETROSPECTIVE ANALYSIS OF PATIENTS WITH SMALL LUNG ADENOCARCINOMA (<2CM) BY NEW WORLD HEALTH ORGANIZATION CLASSIFICATION
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Background: The median follow-up time was 20 months (range: 6 to 55 months). The mean Krebs von den Lungen-6 (KL-6) level was 1608 ± 1025 U/mL. The mean tumor size was 24 ± 7mm. The mean percentage of predicted diffusing capacity for carbon monoxide (DLCO) was 37±27%. Thirty and 90-day mortality was 0 and 18%, respectively. Two patients required chest tube drainage because of severe pneumothorax. Acute exacerbation of IPF occurred in two patients (18%). The use of oral steroids and need for chest tube drainage were predictors of higher mortality (p < 0.05) and higher incidence of acute exacerbation of IPF (p < 0.05). However, higher level of KL-6 and low percentage of DLCO were not significant risk factors of mortality or acute exacerbation of IPF. Local progression-free survival at 1, 2 and 3 year was 51, 41 and 31%, respectively. Conclusion: Percutaneous cryoablation for lung cancer patients with IPF provoked acute exacerbation of IPF in 18% of the patients. The use of oral steroids and need for chest tube drainage were predictors of higher mortality and higher incidence of acute exacerbation of IPF.

Keywords: lung cancer, complications, cryoablation
Background: We have recently demonstrated that the presence of the Spread Through Air Spaces (STAS) and the variety of histologic subtypes increase the risk of recurrence after resection for small lung adenocarcinoma (ADC). Currently, the new World Health Organization classification of lung cancers was revised and newly prescribed to describe the presence of each histologic subtypes and STAS. The purpose of this study is to examine the risk factor for recurrence other than TNM staging by analyzing clinical information retrospectively. Methods: All available tumor slides from patients with clinical stage I, therapy-naive, surgically resected solitary lung ADC ≤2 cm in size (1998-2015) were reviewed. Each tumor was evaluated by comprehensive histologic subtyping, and the percentage of each histologic component was recorded in defined as the spread of tumor cells into air spaces in the lung parenchyma adjacent to the main tumor according to the WHO classification. Recurrence-free probability (RFP) was estimated using the Kaplan-Meier method. Results: 354 patients met inclusion criteria (52.3% men; median age: 67yrs; median tumor size: 1.3cm; 325 stage IA/29 stage IB; 91 patients in Group A, 103 in Group B, 154 in Group C). Matching based on propensity score produced 38, 47, and 49 paired patients in Group A, B, and C, respectively. In Group A and B, there was no significant difference in OS and FFR between patients who received adjuvant chemotherapy and those who did not. In Group C, patients who received platinum-based adjuvant chemotherapy and those who did not. Conclusion: The patients of small ADC with STAS or solid component had worse prognosis. The patients after sublobar resection with solid component should be considered a factor to upgrade the pathologically defined T stage.

Keywords: solid component, Adenocarcinoma, Spread Through Air Spaces, histologic subtypes

OA12: SBRT AND OTHER ISSUES IN EARLY STAGE NSCLC
TUESDAY, DECEMBER 6, 2016 - 11:00-12:30

OA12.07 SELECTION FOR ADJUVANT CHEMOTHERAPY IN STAGE IB NON-SMALL CELL LUNG CANCER: A PROPENSITY SCORE-MATCHED ANALYSIS
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Background: The newly proposed International Association for the Study of Lung Cancer (IASLC) staging system reclassified T2aN0M0 tumors greater than 4 cm as stage IIB instead of stage II. This study investigated the role of adjuvant chemotherapy in pathologic stage IB non-small cell lung cancer (NSCLC). Methods: The patients with pathologic T2aN0M0 NSCLC who underwent complete resection between 2001 and 2013 were identified from prospectively maintained databases, and classified into three groups based on tumor size; A (<3.0 cm, n = 205), B (3.1-4.0 cm, n = 264), and C (>4.0 cm, n = 254). After propensity score matching, overall survival (OS) and freedom from recurrence (FFR) were compared between each group of paired patients who received platinum-based adjuvant chemotherapy and those who did not. Results: Among the 733 patients, 134 patients (18.5%) received adjuvant chemotherapy: Group A, 38 (18.5%) patients; Group B, 47 (17.8%); and Group C, 49 (19.3%). Matching based on propensity score produced 38, 47, and 49 paired patients in Group A, B, and C, respectively. In Group A and B, there was no significant difference in OS and FFR between patients who received adjuvant chemotherapy and those who did not. Conclusion: The patients of small ADC with STAS or solid component had worse prognosis. The patients after sublobar resection with solid component should be made up following closely. We propose that the presence of these factors should be considered a factor to upgrade the pathologically defined T stage.

Keywords: solid component, Adenocarcinoma, Spread Through Air Spaces, histologic subtypes

SESSION OA13: IMMUNOTHERAPY IN MALIGNANT PLEURAL MESOTHELIOMA: CURRENT STATUS OF TRIALS AND NEW APPROACHES
TUESDAY, DECEMBER 6, 2016 - 14:15-15:45

OA13.01 A PHASE II STUDY OF NIVELUMAB IN MALIGNANT PLEURAL MESOTHELIOMA (NIVOMEL): WITH TRANSLATIONAL RESEARCH (TR) BIOPSY
Josine Quispel-Janssen1, Giulia Zago1, Robert Schouten2, Wienieke Buikhuisen3, Kim Monkhorst1, Eric Thunissen1, Paul Baas2
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This abstract is under embargo until December 6, 2016 at 07:00 CET.

OA13.02 PHASE II TRIAL OF PEMBROLIZUMAB IN PATIENTS WITH MALIGNANT MESOTHELIOMA (MM): INTERIM ANALYSIS
Hedy Kindler1, Theodore Karrison2, Yi-Hung Carol Tan1, Buerkley Rose1, Mehwish Ahmad1, Christopher Straus1, Robert Sargent2, Tanguy Seiwert1
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Background: Pembrolizumab showed significant activity in PD-L1+ MM in a phase IB study (Alley, 2015). We are conducting a phase II trial (NCT02399371) of pembrolizumab in previously-treated MM patients to further characterize its activity in a larger, non-selected population, determine a PD-L1 expression threshold, and interrogate the microenvironment. Methods: Eligible patients have histologically-confirmed pleural or peritoneal MM, measurable disease, PS 0-1, disease progression on/after pemetrexed/platinum, ≥2 prior regimens, normal organ function, and available tissue. Patients receive 200 mg pembrolizumab IV Q21 days and CT scans Q9 weeks. Primary objectives:
PD-L1–positive MPM. Responses from pembrolizumab in patients with MPM were durable; the 6.2% 12-month OS rate in this mostly pretreated patient population warrants further investigation. Long-term administration of pembrolizumab is feasible in patients with MPM, and no new safety signals were identified.

Keywords: Mesothelioma, pembrolizumab, Immunotherapy, anti–PD-1

OA13.04 AUTOLOGOUS DENDRITIC CELLS LOADED WITH ALLOGENEIC TUMOR CELL LYSAZE (HERALY?S) IN PATIENTS WITH MALIGNANT PLEURAL MESOTHELIOMA: CURRENT STATUS OF TRIALS AND NEW APPROACHES

OA13.05 SOMATIC GENETIC ALTERATIONS AND IMMUNE MICROENVIRONMENT IN MALIGNANT PLEURAL MESOTHELIOMA

Keywords: T cell receptor, Somatic mutation, malignant pleural mesothelioma, sequencing
SESSION OA14: NURSES IN CARE FOR LUNG CANCER AND IN RESEARCH
TUESDAY, DECEMBER 6, 2016 - 16:00-17:30

OA14.01 ACCEPTABILITY OF AN ADVANCED PRACTICE NURSE IN LUNG CANCER BY HEALTH PROFESSIONALS AND PATIENTS: A QUALITATIVE EXPLORATION
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Background: The advanced practice nurse in lung cancer (APNLC) has shown to play a key role in meeting the complex supportive care needs of patients with lung cancer. Nurses working in novel advanced practice nursing (APN) roles encounter a range of barriers to effective practice particularly in countries without an existing regulation of these novel roles. Being accepted by patients and healthcare professionals (HCPs) is fundamental for successful role implementation. The University Hospital of Lausanne (CHUV) was the first comprehensive cancer center in Switzerland to integrate an APNLC into the specialized multidisciplinary team (MDT) of the thoracic cancer center. To overcome barriers to implementing the APNLC role and promote its acceptance by the hospital’s stakeholders, a new role was developed. The aim of this study was to assess the acceptance by patients and HCPs of the APNLC role from the perspective of the MDT and the patients cared for by the APNLC. Methods: This qualitative study was part of a larger implementation study (ClinicalTrials.gov, number: NCT03262204). During summer 2015, we conducted focus groups and semi-structured interviews in the thoracic cancer center of CHUV. Participants were purposefully sampled and included patients with lung cancer (n=4) and HCPs from the MDT (physicians (n=6), nurses (n=5)), a social worker and the APNLC. Semi-structured individual interviews were conducted to examine the perspectives of patients and the APNLC. Focus groups were employed to gather perspectives from different stakeholders. Results: Three main themes emerged describing the acceptability of the APNLC: “role identification”, “role-specific contribution” and “flexible service provision”. Physicians and patients identified the specific APNLC role within the MDT. In particular, they valued specific contributions to continuity of care, psychosocial support and self-management of symptoms. Nurses perceived the APNLC role as overlapping with the traditional oncology nurse role. They were concerned about losing part of their traditional role. Flexibility in service provision was seen as strength of the APNLC role yet also posed organizational challenges related to the work load. Conclusion: The new APNLC role appears to be well-accepted by patients and physicians. Barriers identified during the implementation of the APNLC role were primarily related to intra-professional and organizational challenges. The intra-professional role tension could challenge the effective implementation of the role. To maximize the acceptability of the new APNLC role, it is fundamental to meet the complex supportive care needs of patients with lung cancer. Nurses working in novel advanced practice nursing (APN) roles encounter a range of barriers to effective practice particularly in countries without an existing regulation of these novel roles. Being accepted by patients and healthcare professionals (HCPs) is fundamental for successful role implementation. The University Hospital of Lausanne (CHUV) was the first comprehensive cancer center in Switzerland to integrate an APNLC into the specialized multidisciplinary team (MDT) of the thoracic cancer center. To overcome barriers to implementing the APNLC role and promote its acceptance by the hospital’s stakeholders, a new role was developed. The aim of this study was to assess the acceptability by patients and HCPs of the APNLC role from the perspective of the MDT and the patients cared for by the APNLC. Methods: This qualitative study was part of a larger implementation study (ClinicalTrials.gov, number: NCT03262204). During summer 2015, we conducted focus groups and semi-structured interviews in the thoracic cancer center of CHUV. Participants were purposefully sampled and included patients with lung cancer (n=4) and HCPs from the MDT (physicians (n=6), nurses (n=5)), a social worker and the APNLC. Semi-structured individual interviews were conducted to examine the perspectives of patients and the APNLC. Focus groups were employed to gather perspectives from different stakeholders. Results: Three main themes emerged describing the acceptability of the APNLC: “role identification”, “role-specific contribution” and “flexible service provision”. Physicians and patients identified the specific APNLC role within the MDT. In particular, they valued specific contributions to continuity of care, psychosocial support and self-management of symptoms. Nurses perceived the APNLC role as overlapping with the traditional oncology nurse role. They were concerned about losing part of their traditional role. 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center network was convened with the goal of developing educational platforms for nursing staff as well as patients. Bringing stakeholders together was felt to be important to increase buy-in across the spectrum of care locations, as well as to ensure that the program was effective and appropriate for all sites. Program components included the following: Education for staff to better identify and manage IrAEs; Development of an electronic nursing flow-sheet to standardize patient assessment and document IrAEs in the lung cancer population; Automatic notification through the EMR to alert staff in non-oncology settings regarding I-O patients. Development of a forum for patient education to better understand I-O therapy and how to identify and manage IrAEs; Development of lung cancer specific telephone triage guidelines. Results: The outcomes of implementing the I-O program included increased patient participation in educational forums and improved patient satisfaction. Incorporation of the I-O assessment flow-sheet and telephone triage guidelines will improve staff competency, as well as standardize documentation and monitoring of IrAEs. These metrics will allow for more accurate tracking of IrAEs throughout the course of treatment. Conclusion: The I-O Integrated Education and Assessment Program standardizes practice across all oncology care delivery sites within our network. This program allows patients to receive the highest level of care at convenient regional locations closer to home, with the goal of maintaining patient safety while maximizing the benefit they may receive from I-O therapies.

Keywords: Education, Allied Health, nursing, Immunotherapy

OA14: NURSES IN CARE FOR LUNG CANCER AND IN RESEARCH
TUESDAY, DECEMBER 6, 2016 - 16:00-17:30

OA14.03 INTEGRATING THERAPIES INTO A SPECIALIST LUNG CANCER NURSING TEAM: AN EVALUATION
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Background: A diagnosis of advanced lung cancer inevitably results in deterioration in both health and functional status. This threatens a person’s independence and dignity and can be a burden to their family and carers. The lung cancer nursing team at Oxford identified a lack of timely therapy provision for their patient group and sought to improve this, concluding that having an integrated therapeutic role (ITP) in the team would significantly expand/diversify the service that could be offered to patients. Lung cancer therapy goals were identified as a) working with patients and carers to anticipate functional need rather than waiting for a crisis to occur b) providing a rapid, flexible and responsive service to those with existing needs and c) working in a keyworker role outside of traditional therapy expertise supporting patients at diagnosis, making treatment decisions and providing information.

Methods: Funding was obtained from Macmillan Cancer Support for a three year project looking at delivering a new model of care. An Advanced Therapist (ATP) was recruited with an ITP background and embedded into the nursing team full time. Referrals were received from all members of the lung cancer MDT, the inpatient team, primary and palliative care. Interventions included home assessment, outpatient clinic review, breathlessness and anxiety management, provision of aids, support, education and advice. Data was gathered from a one year period where there were 305 new lung cancer diagnoses. 165 (54%) patients had identified therapy needs. A further 40 (13%) patients were seen by the ATP as part of her generic keyworker role. 205 referrals resulted in a total of 1005 interventions averaging 5 per person. Interventions were allocated to half a day. The value of the role was measured in three ways: User Feedback and Audit/evaluation tools and developing patient information leaflets. The seven most important steps in developing a lung cancer nurse-led clinic are: Aims and Objectives, Planning and Consultation, Multidisciplinary Support, Infrastructure, promoting the nurse-led service, Professional Development and Evaluation. These formed the basis of this framework.

Conclusion: NICE (2011), suggests that patients should be offered a “follow-up lead by a LCNS”. However, nurse-led clinics are challenging and there are many practical and emotional hurdles to be overcome. This framework supports LCNSs in developing and evaluating nurse-led clinics. It gives clear guidance to be considered when developing and new service as well as advising on audit/evaluation tools and developing patient information leaflets.

Keywords: Nurse-Led Clinic Framework Evaluation

OA14.06 THE ROLE OF A MULTI-DISCIPLINARY TEAM APPROACH TO EARLY REHABILITATION AND SYMPTOM MANAGEMENT IN THORACIC ONCOLOGY
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Background: In the United Kingdom thoracic cancer is mainly diagnosed in an older population, who generally have significant co-morbidities, and advanced stage disease. Due to this, they experience high levels of disease burden, both physical and psychological, impacting on individuals’ functional independence and quality of life (QoL). The national governing bodies, such as NICE and LCA, recommend that all patients should have access to an Holistic Needs Assessment (HNA) and Individualized Support Services. Guy’s & St Thomas’ NHS Foundation Trust (GSTFT) have developed a multidisciplinary team (MDT), consisting of Dietetics, Occupational Therapy (OT) and Physiotherapy (PT), who are present within the outpatient thoracic oncology clinics and aim to address the rehabilitation and supportive care needs of all patients. Methods: All new thoracic oncology patients attending outpatient consultant lead clinics at GSTFT were offered an HNA, in order to identify their individual concerns/needs. The assessments are completed by the MDT and individual intervention plans created. Over a three-month period, January to March 2015, data was collected on patient’s diagnosis, treatment offered, treatment intent, symptom concerns, QoL indicators. Outcomes: 0% MDT referrals and mortality. Results: 82 patients completed the assessments, of these 85% reported unmet needs/concerns. The main tumour types seen were Adenocarcinoma, Squamous cell carcinoma, mesothelioma and small cell lung cancer. Of those reporting symptoms the most common were: breathlessness (55%), fatigue (52%), reduced appetite (43%), weight loss (41%), pain (37%),
emotions/mood (33%), sleep concerns (33%), and reduced mobility (32%). 69 patients had onward referrals to supportive care services. The most common referrals were; DT (65%), PT (60%), Dietitian (43%), and patient information (38%). 66% of patients were provided with on the spot MDT intervention.

Conclusion: Providing thoracic oncology patients access to an MDT service on their initial oncology visit, has enabled early identification of the key symptoms this patient group experience, as well as the need for allied health services. This has supported the role of early rehabilitation as being integral to improving patient’s level of symptom burden and QoL. Moving forward it would be beneficial to do a comparative study of the symptoms and intervention needs of this patient group over a longitudinal analysis, with the aim of showing the impact of early rehabilitation on patient’s QoL, survivorship, and life expectancy.

Keywords: Rehabilitation, Multi-disciplinary, symptom, supportive care

OA4: NURSES IN CARE FOR LUNG CANCER AND IN RESEARCH
TUESDAY, DECEMBER 6, 2016 - 16:00-17:30

OA4.07 THE RELATIONSHIP BETWEEN LUNG CANCER STIGMA AND PATIENT REPORTED OUTCOMES

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Background: Patients with lung cancer (LC) report lower quality of life (QoL) and higher levels of psychological distress compared to other cancer populations (Hewitt et al, 2013). Lung cancer-related stigma (LCS) may compromise these findings. Evidence from studies in the United States has shown associations between LCS and lower QoL, higher symptom burden and higher levels of anxiety and depression (Cataldo et al, 2013). Whether these associations exist in people diagnosed with LC in the United Kingdom is unknown. Therefore this study explored the prevalence of LCS and its relationship with patient outcomes as well as QoL in a Scottish population.

Methods: This study was a cross-sectional study. Patients (n=201) diagnosed with LC were recruited by health care professionals at follow-up clinics at four hospitals in Scotland. Participants completed questionnaires to collect demographic data and assess perceived LCS, QoL, symptom severity and level of depression. Clinical data was collected by casenote review. Bivariate correlations were performed to investigate the relationship between stigma, demographics, and patient outcomes. Multiple regression further explored the individual contributions of LCS on LC burden and quality of life.

Results: Participants had a mean age of 69 years (range 41-89 years), 46.8% were males, 92.0% were ever smokers, 17.9% current smokers. The mean LCS score was 53.1 (SD=14.1, range 31-124.). There were significant correlations between higher LCS and lower QoL (r=−0.28, p<0.001), being a current smoker (r=0.17, p<0.05), female sex (r=0.15, p=0.05) depression (r=0.40, p<0.001), symptom burden (r=2.60, p<0.001), and QoL (r=0.52, p<0.001). Multiple regression revealed an overall model that explained 30.6% of the total variance of stigma (F=14.82, p<0.001). Perceived stigma also accounted for significant unique variance in QoL (4.3%, p<0.001) and depression (3.6%, p<0.001) above and beyond that accounted for by relevant variables. No part of the relationship between LCS and symptom burden was found. Conclusion: Stigma was correlated with depression, and QoL. Therefore, it is expected that depression and stigma share some of the explanation of variance of QoL. Nevertheless, stigma was found to have a unique contribution on QoL, and on depression. With this in mind, management of patients with LC could determine the patients’ experience of stigma to tailor treatment plans to improve QoL and psychosocial outcomes. Being younger was correlated with higher LCS. This might reflect changed attitudes toward smoking due to changed marketing strategies in the 1960s.

Keywords: Lung Cancer Stigma, patient reported outcomes, quality of life, supportive care

SESSION OA5: SUBLOBAR RESECTIONS FOR EARLY STAGE NSCLC
TUESDAY, DECEMBER 6, 2016 - 16:00-17:30

OA5.01 LIMITED RESSECTION TRIAL FOR PULMONARY SUB-SOLID NODULES: CASE SELECTION BASED ON HIGH RESOLUTION CT: OUTCOME AT MEDIAN FOLLOW-UP OF 105 MONTHS

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Background: The objective of this study is to confirm limited resection efficacy as radical surgery in patients with minimally invasive lung cancer as indicated by high-resolution (HR) computed tomography (CT), and to confirm intraoperative cytology as a negative margin indicator and reliable margin non-recurrence predictor. Methods: Enrollment required patients with a tumor ≤2 cm in diameter, diagnosed or suspected as a clinical TNM0 carcinoma in the lung periphery based on a CT scan. They had to have a HRCT scan indicating a sub-solid nodule with tumor disappearance ratio, TDR < 0.5. (TDR = 1 - DM/DL, DM: maximum tumor diameter on mediastinal settings, DL: maximum tumor diameter on lung settings). Patients unfit for lobectomy and systematic lymph node dissection were excluded. We performed a wedge or segmental resection. The used stapling cartridges were washed with saline, which was cytologically evaluated. If cytology results were negative, additional margin was resected, and cytologic examination repeated. If the second exam was positive, a routine lobectomy and systematic lymph node dissection was performed. We aimed at enrolling 100 patients. The primary endpoint is 10-year local recurrence free survival rate. Results: This prospective study started in November 2003, and 101 patients were enrolled in 6 years. Of them, 99 were eligible for analysis. The mean age was 62 years (range: 30-75), and 60 were women. There were 11 Noguchi type A tumors, 54 type B tumors, 26 type C tumors, one type D tumor, one malignant lymphoma, 3 hyperplastic lesions, and 3 inflammatory fibroses. None of the 93 malignant nodules showed any vessel invasion although no positive cytology results were obtained, pathologically positive margin was reported after surgery in one type C patient. He later underwent a routine lobectomy and systematic lymph node dissection. There was no clear correlation between tumor size, TDR, and Noguchi subtype. No mortality occurred, but one patient developed postoperative pneumothorax and pneumonia, and another hemorrhagic gastric ulcer. With a median follow-up period of 105 months (range: 72-129) as of June 2016, there have been no recurrences, but one patient died for unspecified cause. Conclusion: We have repeatedly warned that delayed cut-end recurrence is possible following limited resection even for small sub-solid lung cancers. So far however, HRCT scans appear to predict non- or minimally invasive sub-solid lung cancers with high reliability, warranting limited resection as curative surgery in this cohort. Intraoperative cytology reliably indicated negative margins and seems to predict freedom from local recurrence.

Keywords: small sub-solid lung cancer, tumor disappearance rate, stapling cartridge laveage cytology, limited resection

OA5.02 SURVIVAL OUTCOMES IN SUBLOBAR RESECTION FOR CLINICAL TNM0 NON- small CELL LUNG CANCER: WEDGE RESECTION OR SEGMENTECTOMY

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Background: Lobectomy remains the standard treatment for early-stage non-small cell lung cancer (NSCLC). In practice, however, sublobar resection has been selectively offered for patients with clinical Stage IA NSCLC as curative treatment. To seek optimal surgical procedure for early stage lung cancer, we carried out retrospective analyses of 2122 patients who had undergone limited resection for c-T1N0M0 NSCLC from 26 institutions of Japanese association for chest surgery. Methods: A total of 1963 patients with lobectomy or other type of surgery were excluded for survival analysis. We retrospectively categorized patients of these nodules on numbers of criteria for CT findings; scores were added according to the dominance of ground glass appearance (GGA); >75% = 2, >75% = 1, and size of tumor; T1a = 0, T1b = 16. Statistical analyses were carried out using propensity-matching and Kaplan-Meier with log-rank testing. Results: We analyzed 11 matched 731 patients for wedge resection and wedge resection with propensity matching. The overall survival (OS) for score 0 group was 90.2% in segmentectomy (n=419) and 94.7% in wedge resection (n=651) (p=0.0351). The disease free survival (DFS) for score 0 group was 90.2% in segmentectomy and 92.7% in wedge resection (p=0.0645). The OS for score 1 group was 93.6% in segmentectomy (n=278) and 80.4% in wedge resection (n=246) (P<0.0001) (Fig. 1). The DFS for score 1 group is 94.1% in segmentectomy and 75.3% in wedge resection (P<0.0001). The OS for scores 2 was 79.1% in segmentectomy (n=34) and 69.2% in wedge resection (n=34) (p=0.109). The DFS for score 2 group was 87.0% in segmentectomy and 58.8%
OA15.03 COMPARISON OF PROGNOSIS BETWEEN LOBECTOMY AND SUBLOBAR RESECTION FOR CLINICAL STAGE I NON-SMALL CELL LUNG CANCER WITH INTERSTITIAL LUNG DISEASE
Yuhihiro Tsutani, Takeshi Mimura, Yuichiro Kai, Masaaki Ito, Yoshinori Handa, Norifumi Tsukbokawa, Keizo Misumi, Hideaki Hanaki, Yoshishiro Miyata, Morihito Okada
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Background: The prognosis after standard lobectomy for non-small cell lung cancer (NSCLC) with interstitial lung disease (ILD) is poor. This study aimed to compare the prognosis after lobectomy and sublobar resection for early NSCLC with ILD. Methods: Among 794 consecutive patients with clinical stage I NSCLC who underwent complete resection, 107 patients with ILD on high-resolution computed tomography (HRCT), which was defined according to the American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Latin American Thoracic Association classification, were identified. Results: Overall survival (OS) was significantly worse for patients with possible usual interstitial pneumonia (UIP) or UIP pattern than those with inconsistent with UIP pattern (3-year OS, 64.5% vs. 82.1%, respectively; P = 0.031). No significant difference existed in OS between lobectomy and sublobar resection for all patients with ILD (3-year OS, 67.1% vs. 81.9%, respectively; P = 0.14). Although in patients with inconsistent with UIP pattern, OS was similar between lobectomy and sublobar resection groups (3-year OS, 81.1% vs. 83.6%, respectively; P = 0.87), OS was better for patients who underwent sublobar resection than lobectomy in patients with possible UIP or UIP patterns (3-year OS, 81.0% vs. 50.5%, respectively; P = 0.059). Multivariate Cox analysis demonstrated that preoperative diffuse capacity of the lung for carbon monoxide (P = 0.018), not the surgical procedure (P = 0.14), was an independent prognostic factor for OS. Conclusion: Sublobar resection can be an alternative choice for clinical stage I NSCLC with ILD especially for UIP or possible UIP patterns on HRCT.

Keywords: non-small cell lung cancer, interstitial lung disease, sublobar resection

OA15.05 ANATOMICAL PULMONARY SEGMENTECTOMY AND SUB-SEGMENTECTOMY FOR LUNG CANCER USING THE NOVEL FLUORESCENCE TECHNIQUE WITH VITAMIN B2
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Background: The identification of an accurate segment is essential for successful anatomical pulmonary segmentectomy. We have previously developed a new fluorescence technique using a PDD endoscope system and vitamin B2 for identification of pulmonary segments in animal experiments. In this study, we applied this technique clinically to examine the efficacy and safety in anatomical pulmonary segmentectomy and sub-segmentectomy for pulmonary malignancies. Methods: Our technique requires setting of the endoscope system (KARL STORZ GmbH and Co., Tuttingen, Germany) as a fluorescence sensing device and vitamin B2 solution as a fluorescent substance. 17 patients with small lung nodules were enrolled in this study. Regarding our surgical technique, after identification of the target segmental or sub-segmental bronchus, vitamin B2 solution is injected via the bronchus. The target segment is identified as a fluorescent segment with the PDD endoscope system. The identified segment is resected with an electric cautery, stapling devices, or combination of them. In case patient’s lung has severe abnormal change such as emphysema or fibrosis, another technique is indicated. After resection of the target segmental or segmental artery, vitaminB2 solution is systemically administered with intravenous injection. The target segment is identified as a defect of fluorescence with the PDD endoscope system. Following outcomes were collected; success rate of identifying the pulmonary segments, pathological evaluation of dissection margin, duration of chest drainage, and perioperative complications. Results: A total of 18 procedures were performed using this technique. Performed segmentectomy or sub-segmentectomy were as follows; Right S1, S2, S3, S2a+3b, S6, S9, Left S1+2, S3, S4+S5, S6, S8+9b, S9+10. Resected nodules were 14 primary lung cancers, 1 MALT lymphoma, 1 metastatic lung cancer, and 2 benign lung nodules. History of primary lung cancer was adenocarcinoma in all 14 cases. Pathological stage of lung cancer was 12 stageT1a (pT1a, pT1b), 1 stageT1b (pT1b), 1 stageT1b (pT1aN1), and 1 stageT1b (pT1N2). The success rate of identifying pulmonary segments was 100%. Dissection of segmental border was performed with only electric cautery in 12 procedures, and with both of electric cautery and stapling device in 6 procedures. In all cases, no cancer cells were found on the resection margin pathologically. Mean drainage time was 1.7 days (1-4 days). Regarding perioperative complications, veno-vagal reflex was occurred after systemic injection of vitaminB2 in one case, and delayed pneumothorax was found in one case. Conclusion: Our novel fluorescence technique involving a PDD endoscope system and vitaminB2 allowed performing accurate and safe pulmonary segmentectomy and sub-segmentectomy.

Keywords: Surgery for lung cancer, Pulmonary segmentectomy, New technique

OA15.06 THE EFFICACY OF LUNG VOLUME ANALYZER FOR MEASURING RESECTIBLE MARGIN IN PULMONARY SEGMENTECTOMY FOR MALIGNANT DISEASES
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Background: Although the confirmation of an appropriate resection margin from the tumor is crucial for reducing the risk of local recurrence after lung segmentectomy for pulmonary malignancies, there has been no method of measurement. We established a novel approach for performing segmentectomy by using an infrared thoracoscope with transbronchial instillation of indocyanine green (ICG), and improved this method by adding an advanced computer technology via lung volume analyzer for obtaining an appropriate resection margin. Methods: Preoperatively, each patient underwent multislice enhanced computed tomography (CT) using 320-slice scanners for pulmonary angiography and virtual bronchoscopy, and to create several virtual segmentectomies by using Volume Analyzer Synapse VINCENT (Fujifilm Co., Tokyo, Japan). We measured the shortest distance from the tumor to the resection margin in each simulated segmentectomy and selected the most appropriate area of sublobar resection with an appropriate resection margin of approximately 2 cm from the tumor. We prospectively performed segmentectomy in 17 patients and compared between simulated distance and actual distance measured from the specimen. Results: The average number of created patterns of virtual segmentectomy in each case was 4.1 ± 1.0. The mean distance of resection margin in selected virtual segmentectomy was 19.3 ± 9.7 mm. On the other hand, actual shortest distance in resected specimen was 25.4 ± 8.1 mm, which was significantly longer than simulated distance (p=0.027). There was no tumor recurrence in all patients. Conclusion: Lung volume analyzer was an excellent tool for selecting an ideal area of sublobar resection with an appropriate resection margin.
Keywords: Infrared thoracoscopy, indocyanine green, lung cancer, virtual segmentectomy

OA15: SUBLOBAR RESECTIONS FOR EARLY STAGE NSCLC
TUESDAY, DECEMBER 6, 2016 - 16:00-17:30

OA15.07 IS NECESSARY COMPLETION LOBECTOMY IN NSCLC (≤ 2CM) WITH VISCERAL PLEURAL INVASION OR LYMPHOVASCULAR INVASION AFTER SUBLOBAR RESECTION? Youngkyu Moon1, Mi Hyung Moon, Young Kyoon Kim, Yoo-Young Lee, Jae Ki Park, Sook Whan Sung
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Background: The standard surgical treatment of stage I non-small cell lung cancer is anatomical lobectomy. However, in some cases, small peripheral lung cancer (≤2cm) is treated by sublobar resection. The purpose of this study was to define the necessity of completion lobectomy when the tumor was revealed as non-small cell lung cancer with pleural invasion or lymphovascular invasion after sublobar resection.

Methods: We retrospectively reviewed 271 consecutive patients who underwent curative resection for stage I non-small cell lung cancer of 2 cm or less. We analyzed clinicopathological findings and survival between two groups with either invasion-positive tumor (tumor with visceral pleural invasion or lymphovascular invasion) or invasion-negative tumor (tumor without visceral pleural invasion and lymphovascular invasion): sublobar resection group and lobectomy group. Results: Except for age and pulmonary function, there were no differences in clinicopathological characteristics between sublobar resection group and lobectomy group with invasion-positive tumor or invasion-negative tumor. There was no difference in the 5-year recurrence-free survival rate between two groups in the invasion-positive tumor and invasion-negative tumor (78.9% vs 79.8%; p=0.928, 80.2% vs 85.4%; p=0.505). In the multivariate analysis, only number of dissected lymph nodes was a significant recurrence-related factor of stage I invasive-positive non-small cell lung cancer (hazard ratio 0.914, 95% confidence interval 0.845-0.988, p=0.023). Sublobar resection was not a risk factor for recurrence.

Conclusion: The survival between sublobar resection group and lobectomy group in small (≤2cm) non-small cell lung cancer with visceral pleural invasion or lymphovascular invasion were not different. Completion lobectomy is not necessary in small lung cancer after sublobar resection whether the tumor has visceral pleural invasion or lymphovascular invasion.

Keywords: visceral pleural invasion, lymphovascular invasion, non-small cell lung cancer, sublobar resection

SESSION OA16: IMPROVING THE QUALITY OF LUNG CANCER CARE - PATIENTS PERSPECTIVE
TUESDAY, DECEMBER 6, 2016 - 16:00-17:30

OA16.01 THE ROLE OF PATIENT GROUPS IN INTEGRATING THE PATIENT VOICE INTO DRUG FUNDING DECISIONS
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Background: The recent emergence of multiple new targeted therapies and immunotherapies has significantly increased options in the systemic treatment of lung cancer (LC). While great news for patients, in the current environment of scarce health care resources, government agencies deliberating on public funding of cancer drugs struggle with ensuring sustainability of the public health system due to increasingly expensive drug costs. In Canada, the Pan-Canadian Oncology Drug Review (pcODR), a program of the Canadian Agency for Drugs and Technologies in Health (CADTH), provides recommendations that informs public funding decisions for cancer drugs. pcOUDR’s recommendations apply an evidence-based deliberative framework which considers the drugs clinical benefit, patient-based values, cost-effectiveness and adoption feasibility. As part of the pcODR review, patient input is integrated into the clinical and economic reports and recommendations. Patient groups, such as Lung Cancer Canada (LCC), can play a pivotal role by synthesizing the evidence gathered from patients and caregivers to inform the pcODR process.

Methods: Both quantitative and qualitative techniques were used to gather data for LCC’s pcODR submissions. A national survey – the Faces of Lung Cancer (FOLC) – illustrated the perceptions and general unmet needs of those living with LC. Focus groups, one-on-one interviews and audits of patient discussion boards gathered the insights of patients and caregivers with experience on the drug under consideration.

Patients were identified through LCC’s Medical Advisory Committee and their networks, clinical trial investigators, outreach to other patient groups and scans of LC patient/caregiver discussion boards. Results: Since 2014, LCC has made five pcODR submissions. 91 patients and 72 caregivers participated in the FOLC survey. The insights of an additional 62 patients and 38 caregivers with experience on the drugs under consideration were gathered qualitatively.

LCC’s submissions describe the emotional, practical and logistical challenges of living with LC, and illustrate the “life impact” of the drug under consideration. Factors not traditionally included in clinical trial design. Conclusion: pcODR’s deliberative process, partnered with LCC’s methodology, may be an effective model to aid public funding discussions of new cancer drugs. pcODR and the reviewers have found patient group submissions valuable in providing lived-experience insight, at times changing perspectives. LCC’s contribution has been strongly reflected in the funding guidance reports. To supplement its process, pcODR recently launched a pilot project to include clinician input in the review process. The impact of the pilot will be assessed as data becomes available.

Keywords: Regulatory-bodies, Patient-group, Public-funding, Patient-input

OA16.02 SHARED DECISION MAKING (SDM) AND PATIENT DECISION AIDS (PDAS) IN LUNG CANCER: SURVEY OF PATIENTS, SIGNIFICANT OTHERS OR CAREGIVERS
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This abstract is under embargo until December 4, 2016 at 07:00 CET.

OA16.03 THE ALCF CENTERS OF EXCELLENCE MODEL DELIVERS A STANDARD OF CARE TO THE COMMUNITY SIMILAR TO ACADEMIC AND RESEARCH CENTERS
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This abstract is under embargo until December 4, 2016 at 07:00 CET.

OA16.05 SOCIOECONOMIC DETERMINANTS OF LATE DIAGNOSIS OF LUNG CANCER IN FRANCE: A NATIONWIDE STUDY (THE TERRITOIRE STUDY)
Pierre Jean Souquet1, Isabelle Durand-Zaleski2, Christos Chouaid3, Didier Debiuvre4, Arnaud Scherpereel5, Jérôme Fernandes2, Virginie Westel3, Cécile Bleinec6, Anne-Francoise Gaudel-Singer7, Kerine Leblanc6, Hervé Lemasson2, Nicolas Oza3, François-Emery Cotté1, Pierre Chaum1
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Background: Socioeconomic disparities in survival of patients with lung cancer have been identified in many countries. The aim of this study was to examine determinants of late diagnosis of lung cancer in France. Methods: All patients with a first diagnosis of lung cancer in 2011 in the National hospitals databases were included. Information on gender, age, presence of metastasis at diagnosis and any significant chronic comorbidities (hypertension, diabetes mellitus, renal insufficiency, and other chronic lung diseases) was retrieved. Based on
municipality of residence, patients were classified by population density, social deprivation, access to general practitioners and pulmonologists. **Results:** We identified 41,015 patients newly diagnosed for lung cancer in French hospitals. Mean age at diagnosis was 66.4 (±11.9) years and 72% patients were men. 53% (N=21,013) patients were metastatic at the time of diagnosis. This rate was higher for patients in public compared to private hospitals (56.1% vs 42.9%, p<0.0001) and in community compared to university hospitals (60.2% vs 49.6%, p<0.0001). Multivariate analysis found that metastases at the time of diagnosis were significantly associated with a younger age (55 years or less, OR: 1.22 [95%CI:1.16–1.29]; p<0.0001), a low access to pulmonologists (OR: 1.13 [95%CI:0.94–1.23]; p=0.004), a rural or semi-rural dwelling (OR: 1.07 [95%CI:1.02–1.13]; p=0.004) and deprived areas (OR: 1.06 [95%CI:1.01–1.11]; p=0.01). Of the 8,413 patients (20%) who were initially admitted through emergency rooms, 68% had metastatic tumors. Multivariate analysis showed significantly higher rate of admission through ER at diagnosis in patients from most deprived areas (OR: 1.44 [95%CI:1.37–1.52]; p<0.0001), rural or semi-rural (OR: 1.25 [95%CI:1.19–1.32]; p=0.0001), with a low access to pulmonologists and general practitioners (OR: 1.24 [95%CI:1.17–1.30]; p<0.0001 and 1.15 [95%CI:1.10–1.23]; p=0.0001, respectively). Gender (male) and presence of comorbidities were also significant determinants of metastatic disease and admission through ER at diagnosis. **Conclusion:** A majority of French patients with lung cancer were initially metastatic at the time of diagnosis and 1 out of 5 were diagnosed following admission through ER. Residential socioeconomic indicators and access to general practitioners and pulmonologists were significantly associated with these indicators of poor outcome.

**Keywords:** diagnosis, inequality, epidemiology, deprivation

**OA16.06 WILLINGNESS FOR MULTIPLE BIOPSIES TO IMPROVE QUALITY OF LUNG CANCER CARE: UNDERSTANDING THE PATIENT PERSPECTIVE**

**Upal Basu Roy**, Susan Mantel, Margery Jacobson, Andrea Ferris 1

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**Background:** In this era of precision medicine, biomarker testing of cancer tissue is sometimes necessary to match the right patient to the right treatment. A patient might need multiple biopsies if there is recurrence of lung cancer, or to determine eligibility for a new drug or participation in a clinical trial. Anecdotal evidence suggests that physicians are unwilling to recommend additional biopsies because they assume that the patients are likely to refuse.

**Methods:** To understand this patient-physician communications gap, we asked 340 lung cancer survivors through an online survey about their willingness to undergo additional biopsies. The survey was fielded through various social media platforms as well as through an independent research panel. Results: Three-quarters of the survivors surveyed indicated their willingness to have an additional biopsy, regardless of whether they reported any pain or complications from their initial biopsy. Specifically, among the survivors who were willing to undergo an additional biopsy:

- Almost all of the survivors (82%) would do so if it would help their health care team to better match treatment to their specific cancer and personalize their care, versus just being told the test was to look for mutations. In other words, understanding the end benefit of having the test is an important piece of communication.

- Although almost 50% reported pain or complications from their initial biopsy, this group indicated equal willingness to have another biopsy as those without any issues.

- If the doctor were to recommend an additional biopsy or a biopsy after the start of treatment, nearly half would **definitely** undergo one. About two-thirds of the survivors felt that their doctor explained the reason for getting their initial biopsy really well.

**Conclusion:** The study reinforces the importance of a patient-centric model in medicine—in which meaningful and timely information is provided to patients to enable them to be partners in their own care. The study has the following implications for different stakeholders:

- **Patients:** To ask their doctor about new treatments and discuss the need for additional biopsies if necessary. Understanding the end benefit of having the test is an important piece of communication.

- **Patient Advocacy Organizations:** To educate patients and physicians about having an open dialogue to help patients become equal partners in their treatment decision-making.

- **Physicians:** To discuss the benefits and the risks of an additional biopsy with their patients and how it may help decide course of treatment.

**Keywords:** biopsy, advocacy, patient preference, Targeted therapy

**SESSION OA17: ASPECTS OF HEALTH POLICIES AND PUBLIC HEALTH**

**TUESDAY, DECEMBER 6, 2016 - 16:00-17:30**

**AO17.01 ESTIMATE OF ECONOMIC IMPACT OF IMMUNE CHECKPOINT INHIBITORS FOR NSCLC RELATIVE TO PD-L1 EXPRESSION IN THE US**

**Pedro Aguilar Jr** 1, Ramon De Mello, Hakaru Tadokoro, Han Babiker, Barbara Gutierres, Gilberto Lopes 2

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**Background:** Delivering high-quality cancer care at an affordable cost is the main challenge for health care professionals and policy makers. Immuno therapy and emphasis on ensuring quality results in NSCLC. PD-L1 expression is being studied as a predictive biomarker. The objective of our study is to assess the economical impact of NIVO and PEMBER on the budget and with the
use of PD-L1 as a biomarker in the US. Methods: We developed a decision-analytic model to determine the cost-effectiveness of PD-L1 assessment and second-line treatment with NIVO or PEMBRO versus docetaxel. The model used outcomes data from RCTs and costs from the US. We included the costs of adverse events and post-progression therapies. Thereafter, we used American epidemiology data to estimate the impact of the treatment.

Results: We included three RCTs (two with NIVO and one with PEMBRO). The estimated number of cases eligible was 37,638. Treating all patients with NIVOLUMAB would cost $1.6 billion dollars each year, increasing total oncology drug expenditure in the US by 4%. Treating only patients with PD-L1 >1% with NIVOLUMAB would cost US$ 850 million each year and would increase total oncology drug expenditure by 2%. However, with such patient selection up to 46% of cases would not be treated and 2,509 fewer life-years would be saved.

The cost of each year of life saved was improved by PD-L1 selection (from US$46 per QALY to US$229 per QALY). However, with such patient selection up to 46% of cases would not be treated and 2,509 fewer life-years would be saved.

Conclusion: The use of PD-L1 expression as a biomarker for treatment with immunotherapy decreases the overall economic impact and the cost per life-year saved. Nevertheless, the number of life-years saved with this technology would be significantly smaller than if we choose to treat all patients. Further study and societal discussion is warranted in order to find the optimal strategy for patient selection.

Keywords: biomarker, Immunotherapy, Cost of Care, Access

OA17: ASPECTS OF HEALTH POLICIES AND PUBLIC HEALTH TUESDAY, DECEMBER 6, 2016 - 16:00-17:30

OA17.02 POTENTIAL HEALTH AND ECONOMIC CONSEQUENCES OF ORGANIZED VS OPPORTUNISTIC LUNG CANCER SCREENING IN CANADA

William Evans, Cindy Gauvreau, Salma Memon, John Gofin, Jason Lacroixe, Michael Wotton, Natalie Fitzgerald, Anthony Miller

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Background: Annual LDCT screening for individuals 55-74 years with >30 pack-year smoking history is supported by evidence from the NSLT but has led to questions of implementation. Compared to organized screening (ORG), opportunistic screening (OPP) may utilize broader entry criteria and not include smoking cessation. Methods: Health and economic impacts of ORG using NSLT entry criteria were modelled using population microsimulation (OnCSim—formerly Canadian Risk Management MoAn R 2.3) and compared to OPP scenarios. We modeled ORG at a participation rate of 30% and 60%, and with and without smoking cessation, compared to various plausible OPP scenarios: younger individuals (40-74 yr); lesser smoking histories (10 or 20 pack-yrs). Outcomes projected to 20 years included incidence, mortality, number of scans, invasive diagnostics for false positives, and screening and treatment costs. A lifetime horizon and 3% discounting were used to estimate the incremental cost-effectiveness ratio (ICER) from a health system perspective. All costs are in 2016 CAD.

Results: A large number of outputs can be presented. At a participation rate of 30%, average annual incremental incident cases of lung cancer with OPP for 40-74 yr-olds with 10 pack-yr histories are higher by 254 over ORG without cessation, and there would be an average 135 fewer deaths annually. However, the annual number of CT scans would increase by 433,000 on average and diagnostic tests for false positive results would increase by 1540. Average annual costs would increase by $141 M compared with ORG without cessation, resulting in an ICER of $253,000/QALY. OPP with

OA17.03 INSURANCE TYPE INFLUENCES STAGE, TREATMENT, AND SURVIVAL IN ASIAN AMERICAN LUNG CANCER PATIENTS

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Background: Effect of insurance type on lung cancer diagnosis, treatment and survival is still under debate in Asian patients living in United States. Methods: A total of 447,167 patients (18 to 113 years), diagnosed with lung cancer between 2004 and 2013 in the Surveillance, Epidemiology, and End Results database were analyzed. Patient demographics and clinical characteristics were compared between Asian and Non-Asian patients. In Asian patients, patient demographics and characteristics were compared among insurance types. Multivariable logistic regression analysis was performed to identify the effect of insurance types on stage at diagnosis and treatment modalities. Multivariable cox’s regression analysis was performed to identify the effect of insurance type on cancer-specific death. Results: Asian were significantly more frequently males (56.7% vs. 53.1%), married (62.2% vs. 50.2%), with Medicaid (17.4% vs. 8.7%), living in rural area (93.6% vs. 86.9%), in a low income county (26.3% vs. 13.4%), and stage 4 at time of diagnosis (51.1% vs. 48.0%) than non-Asian patients (all p < 0.001). Among 26,884 Asian lung cancer patients, uninsured was significant younger (61.1±10.8 years) than non-Medicaid (65.1±11.9 years) and Medicaid (70.7±11.7 years), p <0.001, more likely single (18.9 % vs. 8.8% vs. 13.0%); living in a high income county (41.8% vs. 30.5% vs. 38.6%); more likely to be stage IV (63.7% vs. 50.0% vs. 51.2%); and not undergo surgery (86.2% vs. 75.4% vs. 82.6%), [all p-value < 0.001]. Localized disease was more frequent in non-Medicaid (21.2%) and Medicaid (17.3%) compared to uninsured (9.0), (p < 0.001). At multivariable analyses, insurance type was not associated with cancer-directed surgery and radiotherapy. Insurance was significantly associated with cancer-specific death (uninsured HR 1.37 95%CI 1.07-1.75; non-Medicaid HR 1.17 95% CI 1.07-1.28 vs Medicaid).

Conclusion: Insurance type affects stage at diagnosis and cancer-specific death but not surgical treatment and radiotherapy in Asian lung cancer patients.

Keywords: Disparities, race, cancer-specific death, insurance

OA17: ASPECTS OF HEALTH POLICIES AND PUBLIC HEALTH TUESDAY, DECEMBER 6, 2016 - 16:00-17:30

OA17.05 SURVIVAL IN A COHORT OF PATIENTS WITH LUNG CANCER:

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THE ROLE OF AGE AND GENDER ON PROGNOSIS
Juliana Franceschini, Sérgio Jamnik, Ilka Santoro
Universidade Federal de São Paulo, São Paulo/Brazil

Background: Lung cancer has a high incidence in Brazil; approximately thirty-four thousand new cases are diagnosed each year. In Brazil, as in other countries, the majority of patients diagnosed with lung cancer are elderly. There are few studies that evaluate demographic and clinical characteristics, disease staging, treatment modalities and survival in young patients, mostly carried out in developed countries. This study aimed to describe these aspects in patients with non-small cell lung cancer (NSCLC) according to age. Methods: Retrospective cohort consisted of patients diagnosed with NSCLC followed in a referral hospital in São Paulo. During the monitoring the survival time was evaluated. Survival functions were calculated using the method of Kaplan-Meier. The survival stratified by age was also obtained, according to distribution of percentages (less than 55, between 55 and 72 years; older than 72 years). Differences between survival curves were determined using the log-rank test. Results: From January 2000 to July 2015 790 patients were followed, 165 aged less than 55 years, 423 between 55 and 72 years and 202 older than 72 years. Higher incidence of adenocarcinoma was seen at the groups up to 72 years. 757 (73%) patients with advanced disease (IIIb-IV) stage were observed. The median five-year survival was 12 months (4-6). The survival of patients in different age groups was not different.

OA17: ASPECTS OF HEALTH POLICIES AND PUBLIC HEALTH TUESDAY, DECEMBER 6, 2016 - 16:00-17:30
OA17.07 TIME FROM THE IDENTIFICATION OF A SUSPICIOUS PULMONARY LESION TO THE TREATMENT OF NON-SMALL CELL LUNG CANCER
Claire Hiles1, Paul Hiles1, Michael Osswald1
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Background: Despite guideline recommendations on time intervals in the care of a lung cancer patient, delays are often experienced. The goal of this study was to quantify time intervals and identify delays in the workup to treatment of non-small cell lung cancer (NSCLC) at our institution. Methods: A retrospective review of all NSCLC cases in the Tumor Registry at a tertiary military medical center diagnosed and treated between July 2011 and July 2014 was performed. Dates of radiographic identification of a suspicious pulmonary lesion, tissue diagnosis, evaluation by the treating specialist, and initial treatment (whether surgery, radiation, chemotherapy, or best supportive care/palliative care) were recorded. Time intervals were calculated from these dates; if any interval was more than 60 days, reasons for delays were recorded. Results: The median time from the identification of a suspicious pulmonary lesion to the treatment of NSCLC was 74 days (range 5-557 days) and the median time from tissue diagnosis to first treatment was 33 days (range 1-252 days) for the 148 patients included in the analysis. Even after excluding outliers, the adjusted median time from the identification of a suspicious pulmonary lesion to the treatment was 71 days. The most common reasons for treatment delay were waiting for consultant evaluations, staging procedures, repeat biopsies, or additional studies (pre-operative risk stratification, molecular testing). Only 1 patient was upstaged from time of diagnosis to first treatment (from IA to IIb following resection).

OA17.07.06 MAKE THE WORLD BEAUTIFUL AND HEALTHY BY MAKING YOUR COUNTRY SMOKE FREE: CASE STUDY BETWEEN ICELAND AND THAILAND?
May Cho
Tobacco Control, Southeast Asia Tobacco Control Alliance, Bangkok/Thailand

Background: Globally, 600,000 non-smokers die due to tobacco related diseases and health care cost for tobacco related diseases are soaring especially in developing countries. Cigarette smoke contains 69 known carcinogens out of 7000 chemicals causing various health problems in children and infants including ear infections, bronchitis, pneumonia, frequent and severe asthma attacks, sudden infant death syndrome and cancer. Secondhand smoke can cause coronary heart disease, stroke and various kinds of cancer including lung cancer in adult. 2006 U.S. Surgeon General Report clearly confirmed that there is no safe level of exposure to secondhand smoke. Therefore, there is a strong need for comprehensive smoke free law in reducing the burden of tobacco use in the world. Methods: “Section not applicable” Results: Iceland is a high income country with a long history of tobacco control. The comprehensive tobacco control law was passed in 1984 which included restriction on smoking in service areas of public and private buildings, premises of health care facilities, schools, workplaces, and in public transport whereas Thailand is an upper middle income country and once had a very high smoking rate (70 percent for male and around 5 percent for female) in early 1970s. Smoking ban in movie theaters and buses ordinance was issued by Bangkok Metropolitan Administration in 1976 followed by the comprehensive interventions including smoke-free areas by the royal Thai government in 1991. As a result, the smoking prevalence went down to 32 percent in Thailand but this still demonstrated that one in three adults in 1991. It was found that the role of government and different civil society organizations in implementing smoke free policies was significant in both countries in this review paper. Although both countries issued smoke free policies, there are still challenges on implementation. Iceland try to overcome the challenges by developing comprehensive system including investigation after complaint and allocating budget for enforcement. Thailand also implemented 100% Smoke-Free Hospitals with the compliance rate of 86.4 percent according to a research in 2010. Thailand established the Thai Health Promotion Foundation (ThaiHealth) in 2001 which allowed Thailand to implement comprehensive tobacco control measures in a sustainable way. ThaiHealth used knowledge generation, social mobilization and policy advocacy called tri-power strategy in achieving the success. Conclusion: This paper concluded that civil society initiative and continuing efforts on tobacco control which leads to adoption of comprehensive tobacco control law is the heart of the success of tobacco control in both countries.

Keywords: smoke free, policy advocacy, role of government in civil society, comprehensive tobacco control law

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<td>Days from suspicious imaging study to tissue diagnosis</td>
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<td>Days from evaluation by treating specialist to first treatment Surgery Radiation Chemotherapy Best supportive care</td>
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OA18.01 POSTOPERATIVE RADIOThERAPY IN THYMIC EPIThEliAL TUMORS: INSIGHTS FROM THE RYTHMIC PROSPECTIVE COHORT
Clémence Basse1, Sébastien Thureau2, Suzanna Bota3, Eric Dansin4, Pascal Alexandre Thomas5, Eric Pichon6, Hervé Léna1, Carole Massabéu1, Christelle Clément-Duchêne7, Gilbert Massard5, Virginie Westine1, François Thillays7, Xavier Quantin2, Olivier Dukhour7, Séverine Danchies5, Delphine Lerouge5, Luc Thiberville5, Benjamin Besse1, Nicolas Girard8
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Background: Thymic Epithelial Tumors (TET) are rare intrathoracic malignancies, for which surgery represents the mainstay of the treatment strategy. Current practice for postoperative mediastinal radiotherapy is highly variable, and there is paucity of prospective, multicentre evidence. RYTHMIC is the nationwide network for TET in France, established in 2012. Whether postoperative radiotherapy (PORT) should be delivered was the most frequent question raised at the RYTHMIC multi-disciplinary tumor board (MTB) over the past 3 years, accounting for 494 (35%) of a total of 1401 questions.

Methods: All consecutive patients for whom postoperative adjuvant radiotherapy was discussed at the RYTHMIC MTB from 2012 to 2015 were identified from the RYTHMIC prospective database. Results: 285 patients were identified, 274 (52%, 48% women) of whom fulfilled inclusion criteria. Average age at time of TET diagnostic was 60 years. TET histology was thymoma in 243 (89%) cases - including type A in 11% of cases, type AB in 28%, type B1 in 17%, type B2 in 29%, and type B3 in 14%, - and thymic carcinoma in 31 (11%) of cases. Complete resection was achieved in 81% of patients. Masaoka-Koga stage was I in 29% of cases, II in 21%, III in 18%, and IV in 11%. Decision of the MTB was consistent with guidelines in 221 (92%) assessable cases. Clinical situations for which PORT was indicated in accordance with guidelines (B1/B2 cases) were thymoma/R0 resection (30 patients), thymoma/R0 resection/stage II (22 patients), thymoma/R0 resection/stage III (22 patients), thymic carcinoma/R1 resection (6 patients), thymic carcinoma/R0 resection (13 patients), thymoma/R0 resection/stage IIA type B3 histology (2 patients). Inconsistencies between decision of the MTB and guidelines - 20 (8%) cases - consisted of abstention related to poor general condition (10 patients), carcinoid histology (2 patients), and discordance in staging (1 patient), and of delivery of radiotherapy related to peroperative tumor fragmentation (2 patients); for 5 patients who received PORT, a clear explanation for inconsistency with guidelines was not found, but those cases were corresponded to MTB's grey zone of guideline. MTB discussion for PORT was actually implemented for 95 (89%) of patients; most frequent reason for not delivering radiotherapy was prolonged delay since surgery. Conclusion: Our data provide with a unique insight into the decision-making process for postoperative radiotherapy in thymic epithelial tumors, highlighting the need for a systematic discussion at an expert MTB, while stressing the value of current available guidelines.

Keywords: Radiotherapy, Adjuvant treatment, Thymoma, Thymic carcinoma

OA18.03 SAFETY AND CLINICAL ACTIVITY OF AVELUMAB (MSB001078C; ANTI-PD-L1) IN PATIENTS WITH ADVANCED THYMIC EPITHELIAL TUMORS (TETS)
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Background: Avelumab (MSB001078C) is a fully human, IgG1 anti-PD-L1 antibody under clinical development. We report safety and clinical activity in patients with relapsed TETs enrolled in a phase I trial (NCT01777200).

Methods: Patients previously treated with one or more standard therapies, with no prior immune checkpoint inhibitors, and with no history of autoimmune disease were eligible. Treatment was administered as a dose of 10-20 mg/kg q2 weeks until disease progression or toxicity. Responses were assessed q6 weeks by RECIST 1.1. Correlative studies included evaluation of tumor cell PD-L1 expression and peripheral blood immune subset analysis. Results: 7 patients with thymoma and 5 with thymic carcinoma (TC) were treated with avelumab; 3 patients with thymoma (2 B3, 1 B2/B3) received avelumab 20 mg/kg; 4 patients with thymoma (1B1, 3 B2) and 1 TC received 10 mg/kg. Two (29%) patients with thymoma had a confirmed partial response (PR); at 20 mg/kg, and 1 at 10 mg/kg, 2 (29%) had confirmed PRs, 2 (29%) stable disease (SD) and 1 (14%) progression (PD). One patient had SD. Most adverse events (AEs) were mild (grade 1 or 2). Grade 3 and 4 AEs were observed in 3 (38%) patients each, and included potential immune-related AEs (irAEs) in 5 cases. irAEs resolved completely with oral steroids in 3 patients, and incompletely in 1 patient. One patient required cyclosporine A for treatment of irAEs, 4 responders experienced irAEs (myositis in 3 patients, all after 1 dose of avelumab, and enteritis in 1 patient). Pre- and post-treatment tumor biopsies were available for analysis of PD-L1 expression and intratumoral immune infiltrates from three patients treated at 20 mg/kg. In one case the post-treatment biopsy showed necrotic tissue with no viable tumor. In the other two cases diffuse, membranous PD-L1 staining of epithelial cells

OA18.02 EVALUATION OF A MODIFIED DOSING REGIMEN (2-WEEKS ON/1-WEEK OFF) OF SUNItINIB AS PART OF A PHASE II TRIAL IN THYMIC CARCINOMA
Arun Rajan1, Chul Kim2, Udayam Guha3, Eva Szabo4, Arlene Bernie5, Linda Sciotto6, John Stippelt7, Jane Trepel8, Seth Steinberg9, Pamela Harris10, Raffit Hassan10, Patrick Loehrer Sr.10
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Background: Sunitinib is active in patients with recurrent thymic carcinoma (TC). We have previously reported an objective response rate of 26% and disease control rate (partial response and stable disease) of 93% in patients with TC when sunitinib is administered at a dose of 50 mg orally once daily for 4 weeks followed by 2 weeks off (4/2 dosing schedule). Grade 3 or 4 treatment-related adverse events (TEAEs) occurring in more than 10% of patients included fatigue, oral mucositis and lymphocytopenia (20% each), and hypertension (13%). Grade 3 decrease in left ventricular ejection fraction (LVEF) was observed in 8% of patients. Alternative dosing regimens have been evaluated in solid tumors to improve tolerability. As part of an ongoing phase II trial (NCT01621568), we evaluated the clinical activity and tolerability of sunitinib in patients with TC using a 2-weeks-on/1-week-off (2/1) dosing regimen. Methods: Patients with progressive TC after at least one prior platinum-containing chemotherapy regimen, measurable disease, and adequate end organ function were enrolled and received sunitinib at a dose of 50 mg orally once daily using a 2/1 schedule until disease progression or development of intolerable adverse events. The primary objective was evaluation of response rate. Tumor assessments were performed every 6 weeks using RECIST version 1.1 and toxicity was assessed every 3 weeks using CTCAE version 4.0. Explorative correlative studies including evaluation of immune cell subsets will be reported separately. Results: Between July 8, 2014 and January 14, 2016, 15 patients were enrolled. Median age was 62 years (range, 41-76), and 33% were male. A median of 4 (range, 1 – 3+) cycles of sunitinib was administered. Among 13 evaluable patients, there was 1 (8%) partial response, 11 (85%) stable disease and 1 (8%) progressive disease. After a median follow-up of 16 months, the median progression-free survival was 5 months and median overall survival was 16 months. Grade 3 or 4 TEAEs occurring in more than 10% of patients included neutropenia (40%), neutropenia and leucopenia (20%), thrombocytopenia and oral mucositis (13%) each. Grade 3 decrease in LVEF was observed in 1 (7%) patient. Conclusion: Sunitinib, administered using a 2/1 dosing schedule, has clinical activity in patients with TC, and the frequency of clinically significant TEAEs (fatigue, mucositis, hypertension) is acceptable. Studies are ongoing to identify novel immunological biomarkers of activity.

Keywords: Sunitinib, Modified dosing regimen, Clinical activity and tolerability, Thymic carcinoma

OA18: NEW INSIGHTS IN THE TREATMENT OF THYMIC MALIGNANCIES WEDNESDAY, DECEMBER 7, 2016 - 11:00-12:30

SESSION OA18: NEW INSIGHTS IN THE TREATMENT OF THYMIC MALIGNANCIES WEDNESDAY, DECEMBER 7, 2016 - 11:00-12:30

OA18.01 POSTOPERATIVE RADIOThERAPY IN THYMIC EPIThEliAL TUMORS: INSIGHTS FROM THE RYTHMIC PROSPECTIVE COHORT

OA18.03 SAFETY AND CLINICAL ACTIVITY OF AVELUMAB (MSB001078C; ANTI-PD-L1) IN PATIENTS WITH ADVANCED THYMIC EPITHELIAL TUMORS (TETS)
was seen in both pre- and post-treatment biopsies. The immune infiltrate consisted of immature T cells in pre-treatment tumor samples in both cases. The post-treatment biopsy showed continued presence of immature T cells in pre-treatment tumor samples in both cases. Decreased CD4+ regulatory T cells and decreased ratio of granulocytic vs. monocytic myeloid-derived suppressor cells was seen post-treatment at the 20mg/kg dose.

Conclusions: Avelumab is active in patients with recurrent thymoma. Further studies will be needed to assess the impact of this treatment on progression-free survival and overall survival in this population.

Keywords: immune checkpoint inhibitor, Thymoma, avelumab

OA18.05 FDG-PET IN THYMIC EPITHELIAL TUMORS: AN EVALUATION OF ONLY RESECTED TUMORS
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1Thoracic Surgery, National Cancer Center Hospital, Tokyo/Japan, 2Thoracic Surgery, Shizuoka Cancer Center, Shizuoka/Japan

Background: 18F-Fluorodeoxyglucose positron emission tomography (FDG-PET) is thought to be useful for differentiating thymic epithelial tumors (TETs). Although there have been many reports on the use of FDG-PET for evaluating TETs, no previous studies have included only resected cases. Therefore, we investigated the relationship between the degree of FDG-uptake in the tumor and the WHO histologic subtype or the tumor stage in tumors with resected TETs. Methods: We retrospectively reviewed FDG-PET findings in 112 patients with TETs (92 with thymomas and 20 with thymic carcinomas) resected at 2 institutes in Japan. The Spearman rank correlation coefficient was used to assess the association between the maximum standardized uptake value (SUV max) in the tumor and both the histologic subtype and tumor stage. The cut-off value of SUV max for differentiating thymoma from thymic carcinoma was calculated using a receiver operating characteristic (ROC) curve analysis. Results: The Table shows the relationship between SUV max in the tumor and the WHO histologic subtype. SUV max according to each tumor stage was 3.9±1.7 (mean ± SD) in stage I (n = 89), 4.7±1.7 in stage II (n = 3), 7.4±2.3 in stage III (n = 11), and 7.6±3.9 in stage IV (n = 9). SUV max was strongly related to both the WHO histologic subtype and tumor stage (Spearman rank correlation coefficient = 0.485 and 0.432, p < 0.001 and 0.000, respectively). The optimal cut-off value of SUV max for differentiating thymoma from thymic carcinoma was 4.6, with a sensitivity of 80% and a specificity of 70%.

Histologic subtype | No. of patients | Mean ± SD | Range
--- | --- | --- | ---
A | 12 | 3.5±1.3 | 1.3–6.3
B1 | 19 | 4.1±0.9 | 2.5–6.5
B2 | 10 | 4.2±1.0 | 2.7–5.9
B3 | 6 | 4.8±2.6 | 2.4–8.6
Thymic carcinoma | 20 | 8.0±4.7 | 3.0–21.8
Total | 112 | 4.5±2.8 | 1.2–21.8

Conclusion: Our results suggest that FDG-PET is useful for differentiating thymoma from thymic carcinoma. Further studies will be needed to assess other potential clinical applications of FDG-PET for the evaluation of TETs.

Keywords: FDG-PET, Thymic epithelial tumors, WHO histologic subtype

OA18: NEW INSIGHTS IN THE TREATMENT OF THYMIC MALIGNANCIES

OA18.07 QUALITY OF RESECTION AND OUTCOME IN STAGE III TETS: THE FRENCH RYTHMIC NETWORK EXPERIENCE
Maria Bluthgen1, Eric Dansin2, Dan Ou1, Hervé Léna1, Julien Mazieres2, Eric Pichon1, François Thillays3, Xavier Quantin2, Youssef Oulkhouir1, Thierry Nguyen1, Luc Thiberville1, Christelle Clément-Duchêne1, Colin Lindsay1, Pascale Mossy2, Thierry Molina3, Nicolas Girard4, Benjamin Béchet5, Pascal Alexandre Thomas6
1Cancer Medicine, Gustave Roussy, Villejuif/France, 2Département de Cancérologie Générale, Centre Oscar Lambret, Lille/France, 3Département de Radiation Oncology, Gustave Roussy, Villejuif/France, 4CHU Rennes-Hôpital Pontchaillou, Rennes/France, 5Hôpital Rangueil, Toulouse/France, 6CHU Tours-Byrnorn, Tours/France, 7Institut de Cancérologie de l'Ouest, St. Herblain/France, 8University Hospital, Strasbourg/France, 9University Hospital, Montpellier/France, 10University Hospital, Caen/France, 11Centre Hospitalier Régional Universitaire Hôpital Jean Minjoz, Besançon/France, 12Centre Hospitalier Universitaire, Rouen/France, 13Cancer Center, Nancy/France, 14French Cooperative Thoracic Intergroup (IFCT), Paris/France, 15University Hospital, Nantes/France, 16Thoracic Oncology, Hospices Civils de Lyon, Lyon/France, 17Department of Cancer Medicine, Gustave Roussy, Villejuif/France, 18University Hospital, Marseille/France

Background: Stage III TET represents a heterogeneous population and their optimal approach remains unclear; most of the available literature is composed of small series spanning over extended periods of time. RYTHMIC (Réseau tumeurs THYMiques et Cancer) is a French nationwide network for TET with the objective of territorial cover by regional expert centers and systematic discussion of patients management at national tumor board. We reviewed our experience in stage III thymic tumors in order to evaluate the value of tumor board recommendations and multidisciplinary approach.

Methods: We conducted a retrospective analysis of patients (pts) with stage III TET discussed at the RYTHMIC tumor board from January 2012 to December 2015. Clinical, pathologic and radiologic data were prospectively collected as part of a central database. Survival rates were based on Kaplan-Meier estimation. Cox proportional hazard models were used to evaluate prognostic factors for disease free survival (DFS) and overall survival (OS). Results: 150 pts were included in the analysis. Median age was 64 years (18 – 91), 56% males, 20 patients (13.3%) had thymic carcinoma and 9 was presented with autoimmune disorder (76%) myasthenia. Local treatment was surgery in 134 pts (90%) followed by radiotherapy (RT) in 90 pts; 26 pts received preoperative chemotherapy (CT). Complete resection rate (R0) was
SESSION OA19: TRANSLATIONAL RESEARCH IN EARLY STAGE NSCLC
WEDNESDAY, DECEMBER 7, 2016 - 11:00-12:30

OA19.01 A STANDARDIZED AND VALIDATION OF PROGNOSTIC GENE EXPRESSION SIGNATURES FOR SQUAMOUS CELL LUNG CARCINOMA BY THE SPECS LUNG CONSORTIUM

William Richards1, Raphael Bueno2, David Beer3, Karla Ballman4, Ramaswamy Govindan5, Ming Tao6, Mark Watson7, Daniel Merrick8, Adriaan Van Bokhoven9, Frances Shepard9, David R. Gandara10, Wilbur Franklin11, David Harpole12, Guoan Chen13, Zhengming Chen13, Lucian Chiriac13, Herman Chui13, Carlo Genova14, Mary Beth Joshi14, Ashley Kowalewski14, Mark Donatis14, Christopher Rivard14, Thomas Sporn11, Fred R. Hirsch14

1Surgery, Brigham and Women Hospital, Boston/MA/United States of America, 2Division of Thoracic Surgery, Brigham and Women’s Hospital/Harvard Medical School, Boston/MA/United States of America, 3Gibs Cancer Center, U. of Michigan, University of Michigan, Ann Arbor/MI/United States of America, 4Biostatistics and Epidemiology, Weill Cornell University, New York/United States of America, 5Medical Oncology, Washington University School of Medicine, St. Louis/MO/ United States of America, 6Princess Margaret Hospital, Toronto/ON/Canada, 7Washington University School of Medicine, St. Louis/MO/United States of America, 8Pathology, University of Colorado Anschutz Medical Campus, Aurora/ CO/United States of America, 9Division of Medical Oncology, University of Colorado Anschutz Medical Campus, Aurora/CO/United States of America, 10Division of Hem-Oncology, UC Davis Comprehensive Cancer Center, Sacramento/CA/United States of America, 11Department of Surgery, Duke University Medical Center, Durham/NC/ United States of America, 12U.O.S. Tumori Polmonari, IRCCS San Martino-Istituto Nazionale Per La Ricerca Sul Cancro, Genova/Italy

Methods: MCP clustering. Results: Among 250 cases meeting entry criteria, median age was 70 (43-92), 161 (65%) were male, and most were former (70%) or current (28%) smokers. Surgery was pneumonectomy: 5%; lobectomy: 74%; sublobar: 18%. Pathologic staging was T1: 49%; T2: 50%; T3: 2%; N0: 88%; N1: 12%, and grade was G1: 4%; G2: 50%; G3: 44%. At followup, 53% of cases were R0, with 24% R1, 20% R2, and 2% R3. Overall survival rate was 88% (95% CI 0.88-0.87) at 5 yrs, and 32% respectively. Gender (HR: 0.2 [95%CI 0.04 – 0.97] p=0.04), histology (HR: 0.19 [95%CI 0.05 – 0.70] p=0.02) and surgery (HR: 0.6 [95%CI 0.10 - 0.20] p<0.001) as primary treatment modality were significant prognostic factors for OS in univariate analysis. Histology (HR: 0.5 [95%CI 0.30 - 0.90] p=0.02) and adjuvant RT (HR: 0.4 [95%CI 0.20 – 1.00] p=0.05) were significantly associated with DFS. Completeness of resection was not associated with survival in our cohort. Conclusion: Surgery followed by radiotherapy improves outcome irrespectively of R0. Stage III TET not candidate to surgery should be reassessed for resection after induction chemotherapy.

Keywords: TETs, stage III, outcome

OA19.02 SEX DIFFERENCES ARE DETECTED IN THE PROFILE OF TUMOR ASSOCIATED INFLAMMATORY CELLS (TAICS) ARE LUNG ADENOCARCINOMA

Carmen Behrens1, Edwin Parra2, Jaime Rodriguez-Canales3, Pamela Villalobos4, Boris Sepesi5, Annika Weissferdt6, Neda Kalhor7, John Heymach8, Cesar Moran9, Don Gibbons10, Ignacio Wistuba11

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Background: A number of studies have characterized TAICS in lung cancer and associated their levels of infiltration with patients’ outcome. There is limited information about the correlation of TAICS infiltration with clinical and pathological features of lung adenocarcinoma. We investigated the association between patterns of tumor infiltrating lymphocytes and macrophages with detailed clinical and pathological features in lung adenocarcinoma.

Methods: We studied archival tumor tissue from 93 surgically resected lung adenocarcinomas, stages I to III. Density of TAICS expressing CD3, CD4, CD8, and CD68 was evaluated using immunohistochemistry (IHC) and image analysis. TAICS density was correlated with tumor’s histological characteristics and patients’ pathological staging. Further, differences in the TAICS infiltrate density of lung adenocarcinomas based on patients’ characteristics. Overall: a) females showed higher levels of CD8+ (P=0.01) and CD3+ (P=0.03) cell density than males; b) smaller tumors (<3cm) showed more CD4+ (P=0.01) and CD3+ (P=0.03) cells than larger tumors.

Keywords: Squamous cell lung cancer, gene expression signature
tumors, and, c) tumors with solid histology pattern showed higher levels of CD8+ cells (P=0.03) cells than non-solid pattern. No overall significant differences on TAICs infiltrates were detected by age, tobacco exposure by pack-years and TTF-1 IHC expression score. However when TAICs density of tumors was examined by sex we found the following: a) in larger tumor (>3cms), females demonstrated higher levels of CD8+ cells (P=0.0077) than males; b) tumors from females older than the median age (63 years) showed more CD4+ (P=0.04), CD8+ (P=0.009) and CD3+ (P=0.042) cells than males; c) tumors from females with >40 pack-years of tobacco history showed significantly higher levels of CD3+ (P=0.004) and CD68+ (P=0.004) cells than males; d) tumors from females with high levels of TTF1 expression (score >150) showed higher levels of CD8+ cells (P=0.03) than males; e) females with tumors having non-solid histology pattern showed higher CD8+ (P=0.02) and CD3+ (P=0.02) cells than males. Finally, tumors expressing low levels of TTF-1 and lower CD4+ cells correlated significantly with worse overall recurrence free survival and overall survival in both males (P=0.0001) and females (P=0.0072).

Conclusion: In lung adenocarcinoma, TAICs infiltration correlates with clinical characteristics of patients and pathological features of tumors, particularly, sex, age, size and TTF-1 expression. Compared with males, lung adenocarcinomas from females showed higher levels of TAICs, particularly at older age, larger tumor size, less exposure to tobacco, and more differentiated histological patterns. (UT Lung SPORE and MD Anderson Moon Shot Program).

Keywords: Lung adenocarcinoma, tumor associated inflammatory cells, sex differences

OA19: TRANSLATIONAL RESEARCH IN EARLY STAGE NSCLC WEDNESDAY, DECEMBER 7, 2016 - 11:00 - 12:30

OA19.03 IDENTIFY LUNG ADENOCARCINOMA IN SITU AMONG PULMONARY MICRO-NODULES THROUGH BLOOD GENE EXPRESSION PROFILES Baihui Han1, Huiming Wang1, Changming Cheng1, Xueyan Zhang1, Wenjia Yang1, FangTie Qian1, Xue Dong1
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Background: The national lung cancer screening test (NLST) confirmed: low dose CT screening could reduce lung cancer mortality. However, the high false-positive rates of LDCT screening, especially the difficulty of diagnosis of micro-nodules with size less than 10 mm highlight the need of complementary diagnostic methods. In this study, we aimed to identify lung cancer-specific genetic signatures in peripheral blood samples of patients with micro-nodules less than 10 mm.

Methods: The blood gene expression profiles of 46 lung cancer patients, 38 pulmonary lesions and 11 healthy individuals were analyzed to identify the lung cancer-specific genetic signatures. The lung cancer patients containing micro-nodules less than 10 mm were surgically and pathologically diagnosed as lung adenocarcinoma in situ. Results: A self-training logistic regression model was used to identify the lung cancer-specific gene signatures as we previously reported. Six genes, including DDXSK1, PSM2, ACTL6A, GMEBI, FAM200B, GEMING, were identified for discriminating lung adenocarcinoma in situ from healthy and benign pulmonary diseases. Patients with the performance of the six-gene panel for diagnosis of lung adenocarcinoma in situ identified was exhibited in Table 1. Through self-training SVM classifier, the logarithmic odds of each sample was calculated and exhibited, in which the cutoff value was set as zero in logarithmic odds for differentiating lung cancer from benign and control group. The predictive model based on this gene panel correctly classified 43 of 46 lung cancer, 39 of 42 benign pulmonary diseases with 93% accuracy, 94% sensitivity, and 93% specificity and 0.97 of the logarithmic odds of each sample was calculated and exhibited, in which the cutoff value was set as zero in logarithmic odds for differentiating lung cancer from benign and control group.

Conclusion: The predictive model based on 6-gene panel (DDXSK1, PSM2, ACTL6A, GMEBI, FAM200B, GEMING) can be used for discriminating between the malignant or benign nodules with size less than 10 mm.

Keywords: gene expression profile, lung adenocarcinoma in situ, micro-nodules

OA19: TRANSLATIONAL RESEARCH IN EARLY STAGE NSCLC WEDNESDAY, DECEMBER 7, 2016 - 11:00 - 12:30

OA19.05 HIGH ONCOFETAL CHONDROITIN SULFATE EXPRESSION IS AN INDEPENDENT PROGNOSTIC FACTOR OF POOR SURVIVAL IN EARLY STAGE NSCLC Zoltan Lohinai1, Htoo Oo1, Gunjan Kumar1, Jeffrey Allen2, Nhan Tran3, Balazs Dorne1, Judit Moldeva1, Glen Weiss1, Mads Daugaard1
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Background: Most human cancers express proteoglycans modified with distinct oncofetal chondroitin sulfate (CS) chains that are normally restricted to placental tissue. Oncofetal CS chains can be conveniently detected and targeted by recombinant VAR2CSA (vVAR2) proteins derived from the malaria parasite Plasmodium falciparum. In the present study, we have analyzed the expression landscape of oncofetal CS modifications in early-stage non-small cell lung cancer (NSCLC).

Methods: Tissue microarrays from four separate patient cohorts representing a total of 493 clinically annotated stage I-II NSCLC cases were stained for oncofetal CS using vVAR2. Data were analyzed for correlation between low and high oncofetal CS presentation by univariate and multivariate methods with respect to EGFR and KRAS mutations, as well as to clinical characteristics including relapse-free survival (RFS) and overall survival (OS).

Results: There were 351 patients with low (HSC 0-1) and 142 with high (HSC 2-3) expressing tumors. We identified 331 adenocarcinomas, 145 squamous cell carcinomas, and 12 cases with other NSCLC subtypes. In stage I patients, 179 stage II cases by AJCC 7th edition. High oncofetal CS expression was significantly associated with shorter RFS (vs. high expressions; 58 vs. 39 months, respectively, p=0.034) and OS (vs. high expressions; 69 vs. 51 months, respectively, p=0.044). High oncofetal CS expression was significantly associated with higher RFS vs. low expression in men (p=0.012), smokers (p=0.011), and in patients with squamous cell tumors (p=0.012). High oncofetal CS was also significantly associated with shorter OS in men (p=0.005) and smokers (p=0.028). There were no significant RFS or OS differences in oncofetal CS expressions when stratifying the patients according to their EGFR or KRAS statuses.

Conclusion: This is the first study showing that high oncofetal CS expression is an independent prognostic factor of poor RFS in NSCLC and validates high oncofetal CS expression as a prognostic factor of poor OS. In contrast to non-smoking males, oncofetal CS appears to be a prognostic for OS in males and smokers. Our work promotes oncofetal CS as a candidate target for vVAR2-based therapeutic intervention in NSCLC patients with poor RFS/OS.

Keywords: prognostic factor, oncofetal chondroitin sulfate expression, Early-stage NSCLC

OA19: TRANSLATIONAL RESEARCH IN EARLY STAGE NSCLC WEDNESDAY, DECEMBER 7, 2016 - 11:00 - 12:30

OA19.06 ADJUVANT CHEMOTHERAPY DECISIONS BASED ON MOLECULAR RISK STATUS IMPROVES OUTCOMES IN EARLY STAGE, NON- Small CELL LUNG CANCER Gayvitt Woodard1, Jane Crockard2, Clara Zoon-Besselink3, Johannes Kratz3, Matthew Gubens4, Thierry Jahan4, Collin Blakely4, Kirk Jones5, Michael Mann6, David Jablons1
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Background: A clinically certified, 14-gene quantitative PCR expression assay has been found to assess mortality risk more accurately than clinicopathologic criteria in early-stage, non-squamous, non-small cell lung cancer (NSCLC). Clinically validated molecular stratification may provide a more informative approach to identify early stage NSCLC patients who are most likely to benefit from chemotherapy than current National Comprehensive Cancer Network (NCCN) high-risk clinicopathologic features.

Methods: Prospective molecular risk stratification by the 14-gene quantitative PCR expression assay was performed on 91 consecutive patients with stage I-IIA non-squamous NSCLC after complete surgical resection at a single institution. Information from molecular profiling was used in conjunction with pathologic stage and NCCN criteria to make adjuvant chemotherapy recommendations. Fisher’s exact test was used to compare recurrence rates, and Kaplan-Meier analysis and log-rank tests were used to evaluate differences in disease-free survival. Results: Median follow-up was 69 years, 57% were female and median follow up was 23±2 months. Among all patients, 33 (36%) met NCCN high-risk criteria for adjuvant chemotherapy and 27 (30%) were molecular high risk. Recommendations for adjuvant chemotherapy were discordant in 18 (55%) of NCCN high-risk patients and in 12 (66%) who were molecular high risk. Twelve (6%) of molecular high-risk patients agreed to receive adjuvant chemotherapy. Whereas recurrence was observed in 33% of molecular high-risk patients who did not receive adjuvant chemotherapy, none of the molecular high-risk patients who underwent chemotherapy recurred (log-rank p=0.001). Conclusion: This prospective single-institution study demonstrates the clinical utility of molecular risk stratification in making early-stage NSCLC to supplement pathologic stage and NCCN guidelines in making adjuvant chemotherapy recommendations. Molecular risk scores better differentiated prospective recurrence rates than did NCCN risk criteria.
Results: survival (OS) according to the type of EGFR mutation. We also analyzed postoperative recurrence-free survival (RFS) and overall survival (OS). The patients with minor EGFR mutations were excluded. We compared their postoperative survivals between two most common mutations, that is, exon 19 deletions (DEL) and exon21 L858R (PM), using multi-institutional data of patients with surgically resected lung adenocarcinomas.

Methods: We retrospectively collected 1,063 consecutive patients who underwent surgical resections for lung adenocarcinoma between 2005 and 2012 in five institutions, and who were examined their EGFR mutation status. The patients with minor EGFR mutations were excluded. We compared their clinicopathological characteristics among DEL, PM, and wild type (WT) group. We also analyzed postoperative recurrence-free survival (RFS) and overall survival (OS) according to the type of EGFR mutation. Results: The number of patients with DEL, PM, and WT was 218 (20.5%), 301 (28.3%), and 544 (51.2%) respectively, and their median follow-up period was 47.6 months. The patients of PM were older and earlier pathological staged than those with DEL, whereas no significant difference was observed among other clinicopathological factors. Five-year DFS and OS of DEL, PM, and WT were 67.3/85.9%, 76.4/88.6%, 59.2/71.5%, respectively, and both survivals of each mutation were significantly better than those of WT. Regarding the difference between DEL and PM, DFS curve of DEL was significantly worse than that of PM (p = 0.027), but OS curves of both mutant weren’t significantly different. (p = 0.16). In multivariate analysis, the type of EGFR mutation (DEL vs PM) was not an independent factor both in RFS and OS. Conclusion: Exon 21 L858R might be a more favorable recurrence-risk factor than exon 19 deletions in patients with surgically resected lung adenocarcinomas.

Keywords: lung adenocarcinoma, postoperative survival, Exon 19 deletions, exon21 L858R

SESSION OA20: IMMUNOTHERAPY AND MARKERS

OA20.01 TUMOR MUTATION BURDEN (TMB) IS ASSOCIATED WITH IMPROVED EFFICACY OF ATEZOLIZUMAB IN 1L AND 2L+ NSCLC PATIENTS

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Background: Epidermal growth factor receptor (EGFR) gene mutation is a robust prognostic factor in patients with advanced lung adenocarcinomas. Recently, on the other hand, there are some reports proposing the difference of survival due to the type of EGFR mutation. In this study, we analyzed the difference of postoperative survivals between two most common mutations, that is, exon 19 deletions (DEL) and exon21 L858R (PM), using multi-institutional data of patients with surgically resected lung adenocarcinomas.

Methods: We retrospectively collected 1,063 consecutive patients who underwent surgical resections for lung adenocarcinoma between 2005 and 2012 in five institutions, and who were examined their EGFR mutation status. The patients with minor EGFR mutations were excluded. We compared their clinicopathological characteristics among DEL, PM, and wild type (WT) group. We also analyzed postoperative recurrence-free survival (RFS) and overall survival (OS) according to the type of EGFR mutation. Results: The number of patients with DEL, PM, and WT was 218 (20.5%), 301 (28.3%), and 544 (51.2%) respectively, and their median follow-up period was 47.6 months. The patients of PM were older and earlier pathological staged than those with DEL, whereas no significant difference was observed among other clinicopathological factors. Five-year DFS and OS of DEL, PM, and WT were 67.3/85.9%, 76.4/88.6%, 59.2/71.5%, respectively, and both survivals of each mutation were significantly better than those of WT. Regarding the difference between DEL and PM, DFS curve of DEL was significantly worse than that of PM (p = 0.027), but OS curves of both mutant weren’t significantly different. (p = 0.16). In multivariate analysis, the type of EGFR mutation (DEL vs PM) was not an independent factor both in RFS and OS. Conclusion: Exon 21 L858R might be a more favorable recurrence-risk factor than exon 19 deletions in patients with surgically resected lung adenocarcinomas.

Keywords: lung adenocarcinoma, postoperative survival, Exon 19 deletions, exon21 L858R

SESSION OA20: IMMUNOTHERAPY AND MARKERS

OA20.02 NEOANTIGEN TARGETING IN NSCLC PATIENTS WITH COMPLETE RESPONSE TO ANTI-PD-1 IMMUNOTHERAPY

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Background: Anti-PD-1 immunotherapy has resulted in durable clinical responses in heavily pretreated patients with non-small cell lung cancer (NSCLC). While NSCLC is typically seen as non-immunogenic, there is a 15-20%
objective response rate and a median duration of response of 17 months in patients treated with the PD-1 inhibitor, nivolumab. This duration of response has not been reported with other systemic therapies in advanced NSCLC. While tumor PD-1 expression may be a biomarker of sensitivity to anti-PD-1 therapy, and the number of somatic mutations may play a role in PD-1 upregulation on T cells, the mechanisms underlying response vs. progressive disease have yet to be fully elucidated. Methods: Whole exome sequencing and mutation-associated neoantigen (MANA) prediction was performed on tumor sections from two advanced NSCLC patients with complete response to nivolumab. Peptides representing MANAs were synthesized and tested against PBMC in a 10-day cultured IFNγ ELISPot assay. Reactive MANAs were assessed in binding and stability assays. TCR sequencing was performed on reactive cell cultures and on DNA obtained from tumor resections to match MANA-reactive TCR clones with clones that were infiltrating the tumor. Results: The mean mutational burden in NSCLC as reported previously is 360 sequence alterations. In our study, patient 1 had 30 sequence alterations and patient 2 had 314. Despite the difference in mutational load, lung cancer-specific survival (LCSS) was quantified by RT-PCR. Prognosis was analyzed by both recurrence free probability (RFP) and lung cancer-specific survival (LCSS). Immunohistochemistry (IHC) using tissue microarrays and mRNA expression (adenocarcinoma, ADC=33; squamous cell carcinoma, SCC=28) and 50 surgically resected, NSCLCs from patients who received and did not receive chemotherapy to determine the characteristics of immune microenvironment of localized, non-small cell lung carcinoma (NSCLC). The clinical efficacy observed with PD-1/PD-L1 inhibitors in metastatic lung cancer (mLCC) has prompted to characterize the immune response in lung tumors treated with chemotherapy. Our goal was to determine the characteristics of immune microenvironment of localized, surgically resected, NSCLCs from patients who received and did not receive neo-adjuvant chemotherapy. Using multiplex immunochemistry (mIF) and image analysis, we investigated anti-PD-1 L1 expression, and quantified tumor-infiltrating lymphocytes (TILs) and tumor-associated macrophages (TAMs). Methods: We studied formalin-fixed and paraffin embedded (FFPE) tumor tissues from 111 stage I and III resected NSCLC, including 61 chemonaive (adenocarcinoma, ADC=33; squamous cell carcinoma, SCC=28) and 50 chemotherapy-treated (ADC=19; SCC=31) cases. Using the Opal 7-color fIHC Kit™ and analyzed using the Vectra™ multispectral microscope and inForm™ Cell Analysis software (Perkin Elmer, Waltham, MA). The markers studied were grouped in two 6-antibody panels: Panel 1, AE1/AE3 pancytokeratin, PD-L1 (clone E1L3N), CD3, CD4, CD8 and CD68; and Panel 2, AE1/AE3, PD1, Granzyme B, FOXP3, CD68/CD163 and CD57. Results: Positive PD-L1 expression (<5%) in malignant cells (MCs) was detected in 48% (n=53/111) of NSCLCs. Overall, chemotherapy-treated tumors showed significantly higher percentages of MCs expressing PD-L1 (median, 18%; P =0.0001) and higher levels of FOXP3-positive cells (P =0.010) and lower density of FOXP3-positive cells (P =0.002) than chemonaive tumors. Chemotherapy-treated SCCs demonstrated higher density of PD-1-positive cells than chemonaive tumors (P =0.004). In chemotherapy-treated cancers, lower levels of CD4 helper T positive cells and tumor associated macrophages (TAMs) CD68-positive cells were associated with worse overall survival (OS; P =0.04 and P =0.005, respectively) in univariate analysis. In chemotherapy-treated ADC patients, lower levels of CD68-positive (P =0.010) and higher levels of FOXP3-positive cells correlated with worse OS (P =0.044). Conclusion: We developed a robust

Keywords: lung cancer, Tumor infiltrating lymphocytes, target therapy, microenvironment

OA20: IMMUNOTHERAPY AND MARKERS
WEDNESDAY, DECEMBER 7, 2016 - 11:00-12:30

OA20.03 TUMORAL IL-7 RECEPTOR IS A POTENTIAL TARGET FOR LUNG ADENOCARCINOMA IMMUNOTHERAPY
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Background: IL-7/IL-7R receptor (IL-7R) interactions have been shown to prevent apoptosis in lung cancer cells and promote stromal macrophage and immune cell homing and differentiation. The aim of this study is to investigate the correlation between tumoral IL-7R expression and stromal pro-tumor immune cells (FoxP3+ Tregs and CD163+ M2 macrophages) and to determine prognostic impact of the combination of these markers in lung adenocarcinomas. Methods: In resected stage I lung adenocarcinoma (n=913; 1995-2009), antigen expression of IL-7R, FoxP3 and CD163 was evaluated by immunohistochemistry (IHC) using tissue microarrays and mRNA expression was quantified by RT-PCR. Prognosis was analyzed by both recurrence free probability (RFP) and lung cancer-specific survival (LCSS). Results: In IHC analysis, high tumoral IL-7R, stromal FoxP3, and stromal CD163 expression were individually associated with lymphatic/vascular invasion, and increasing percentage of positive solid histological pattern. A correlation was seen between IL-7R, FoxP3 and CD163 expression by mRNA and IHC analyses (Figure1). The co-existence of high expression of these 3 markers was found in 16% of patients and was associated with worse outcomes (Figure2). In multivariable analysis, triple marker co-existence was an independent risk factor for RFP (p=0.004) and LCSS (p=0.008). Conclusion: Tumor IL-7 receptor is a potential target for lung adenocarcinoma immunotherapy.

OA20.05 THE INFLUENCE OF NEOADJUVANT CHEMOTHERAPY, ON IMMUNE RESPONSE PROFILE IN NON-SMALL CELL LUNG CARCINOMAS
Edwin Parra1, Jaime Rodriguez-Canales2, Carmen Behrens3, Mei Jiang1, Apar Pataar4, Arelene Corea5, Stephen Swisher1, Boris Sepesi6, Annika Wunderfeldt1, Neda Koltor1, William Williamson Jr7, Jack Lee8, John Heyes9, Cesar Morani1, Jianjun Zhang1, Don Lynn Gibbons2, Ignacio Wistuba2

Background: The clinical efficacy observed with PD-1/PD-L1 inhibitors in metastatic lung cancer (mLCC) has prompted to characterize the immune response in lung tumors treated with chemotherapy. Our goal was to determine the characteristics of immune microenvironment of localized, surgically resected, NSCLCs from patients who received and did not receive neo-adjuvant chemotherapy. Using multiplex immunofluorescence (mIF) and image analysis, we investigated anti-PD-1 L1 expression, and quantified tumor-infiltrating lymphocytes (TILs) and tumor-associated macrophages (TAMs). Methods: We studied formalin-fixed and paraffin embedded (FFPE) tumor tissues from 111 stage II and III resected NSCLC, including 61 chemonaive (adenocarcinoma, ADC=33; squamous cell carcinoma, SCC=28) and 50 chemotherapy-treated (ADC=19; SCC=31) cases. Using the Opal 7-color fIHC Kit™ and analyzed using the Vectra™ multispectral microscope and inForm™ Cell Analysis software (Perkin Elmer, Waltham, MA). The markers studied were grouped in two 6-antibody panels: Panel 1, AE1/AE3 pancytokeratin, PD-L1 (clone E1L3N), CD3, CD4, CD8 and CD68; and Panel 2, AE1/AE3, PD1, Granzyme B, FOXP3, CD68/CD163 and CD57. Positive PD-L1 expression (<5%) in malignant cells (MCs) was detected in 48% (n=53/111) of NSCLCs. Overall, chemotherapy-treated tumors showed significantly higher percentages of MCs expressing PD-L1 (median, 18%; P =0.0001) and higher levels of FOXP3-positive cells (P =0.010) and lower density of FOXP3-positive cells (P =0.002) than chemonaive tumors. Chemotherapy-treated SCCs demonstrated higher density of PD-1-positive cells than chemonaive tumors (P =0.004). In chemotherapy-treated cancers, lower levels of CD4 helper T positive cells and tumor associated macrophages (TAMs) CD68-positive cells were associated with worse overall survival (OS; P =0.04 and P =0.005, respectively) in univariate analysis. In chemotherapy-treated ADC patients, lower levels of CD68-positive (P =0.010) and higher levels of FOXP3-positive cells correlated with worse OS (P =0.044). Conclusion: We developed a robust

Keywords: Immunotherapy, Neoantigens, T cells, Anti-PD-1
mIF panel of 10 markers to study inflammatory cells infiltrates in FFPE NSCLC tumor tissues. Chemotherapy-treated NSCLCs exhibited higher levels of PD-L1 expression and T cell subsets compared to chemo-naive tumors, suggesting that the chemotherapy activates specific immune response mechanisms in lung cancer. (Supported by CPRIT MIRA and UT Lung SPOR grants, and MD Anderson Moon Shot Program).

Keywords: Multiplex Immunofluorescence, neoadjuvant chemotherapy, Non-small cell lung carcinoma, Immune Response Profile

OA20: IMMUNOTHERAPY AND MARKERS
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OA20.06 PROSPECTIVE IMMUNOMICROSCOPIC PROFILING OF NON-SMALL CELL LUNG CANCER - THE ICON PROJECT
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Background: Previous attempts to define tumor and stromal immunologic environment in non-small cell lung cancer (NSCLC) utilized archival tissue. We established prospective comprehensive immunomicroscopic profiling protocol in NSCLC (ICON Project). The goal is to integrate immunogenic, genomic, transcriptic, proteomic, demographic, clinical, pathologic, and outcome data from 100 surgically resected early stage NSCLC. Methods: Tumor and normal lung tissue are collected at the time of surgery, blood samples before and after surgery. Tumor samples are processed for tumor infiltrating lymphocyte (TILs) isolation and expansion; development of patient derived xenografts (PDx), immunohistochemical immune markers, and immunoproteinidose profiling. Blood samples are analyzed with flow cytometry. Results: 57 patients with median age of 65 years (27 males) have been enrolled within 5 months, of which 33 (66%) contributed samples to the study. Four were never smokers, with others being former or current smokers. Majority (N>27) had adenocarcinoma, squamous cell carcinoma, and 2 pleomorphic carcinoma. 15 patients had stage 1, 11 stage II, and 7 stage III disease, 5 patients received induction chemotherapy. Median tumor size was 3.5 cm and 29 underwent R0 and 4 R1 resection. Pre-REP TIL expansion was successful in the majority of samples (68.2%, n=22). Twelve PDx models with a take rate of 40% have been generated. Interim analysis of tumor samples by IHC demonstrated higher median distribution of all cell types: CD3+ T cells, cytotoxic T cells CD8+, PD1+ cells, tumor associated macrophages (TAM) CD68+, TAM CD68+PD-L1+, CD20+B cells, memory T cells CD45RO, natural killer cells CD57+, regulatory FOXP3+ T cells, and cytotoxic granzyme B cells (cells/mm²) in the stroma as compared to the tumor compartment. Intra-tumoral regulatory FOXP3+ T cells were more abundant in squamous cell carcinomas compared to adenocarcinomas (median 312 vs 51 cells/mm², p = 0.05). Higher concentration of intra-tumoral CD68+PD-L1 expressing cells was observed following neoadjuvant chemotherapy (median 97 vs 60 cells/mm² no chemo; p = 0.077), as was the concentration of memory T cells CD45RO (median 129 vs 30 cells/mm², no chemo; p = 0.077). Mass spectrometry-based immunopeptide analysis identified several thousand peptides, of which 4 promising antigens have been chosen for further development as immunotherapeutic T cell targets. Conclusion: The ICON is an ongoing, ambitious prospective project that aims to define the baseline immunologic characteristics of surgically resectable NSCLC. The rapid enrollment illustrates the enthusiasm for tumor immunoprofiling amongst patients and physicians alike. Data from this patient cohort will serve as a baseline comparison for upcoming neoadjuvant immunotherapy trials.

Keywords: NSCLC, immunomic, genomic, TILs

OA20: IMMUNOTHERAPY AND MARKERS
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OA20.07 HHLA2, A NEW IMMUNE CHECKPOINT MEMBER OF THE B7 FAMILY, IS WIDELY EXPRESSED IN HUMAN LUNG CANCER AND ASSOCIATED WITH MUTATIONAL STATUS
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Background: Immunotherapy with antibodies against B7/CD28 family members, including PD-1, PD-L1, and CTLA-4 has shifted the treatment paradigm for non-small-cell lung carcinoma (NSCLC) with improved clinical outcome. HHLA2 is a newly discovered member of the family. By regulating T-cell function, HHLA2 could contribute to tumor immune suppression and thus be a novel target for cancer immunotherapy. There is limited information and critical need to characterize its expression profile and clinical significance in NSCLC. Methods: We performed immunohistochemistry with an HHLA2-specific antibody (clone S66:1) using tissue microarrays constructed from 679 NSCLC tumor tissues, including 392 cases in the discovery set and 287 cases in the validation cohort. We also studied clinicopathological characteristics of these patients. Results: Overall, HHLA2 was not detected in most of normal lung tissue but expressed in 66% of NSCLC across different subtypes. In particular, EGFR-mutated NSCLC was significantly associated with higher tumor HHLA2 expression in both discovery (EGFR vs. WT: 76% vs. 53%, P=0.01) and validation cohorts (89% vs. 69%, P=0.01). In one of the two cohorts, HHLA2 expression was higher in lung adenocarcinoma as compared to squamous and large cell histology, non-Hispanic White vs. Hispanics, and tumors with high tumor infiltrating lymphocyte (TIL) density. In the multivariate analysis, EGFR mutation status and high TIL intensity were independently associated with HHLA2 expression in lung adenocarcinoma. Conclusion: HHLA2 is widely expressed in NSCLC and is associated with EGFR mutation and high TILs in lung adenocarcinoma. It is potentially a novel target for lung cancer immunotherapy.

Keywords: immune checkpoint, lung cancer, HHLA2, mutation

SESSION OA21: PALLIATIVE AND SUPPORTIVE CARE FOR LUNG CANCER PATIENTS
WEDNESDAY, DECEMBER 7, 2016 - 11:00-12:30

OA21.01 POOLED ANALYSIS OF THE INCIDENCE AND RISK OF TREATMENT-RELATED PNEUMONITIS WITH ANTI-PD-1/PD-L1 THERAPIES IN CANCER PATIENTS
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Background: Blockade of programmed death 1 (PD-1), or its ligand, PD-L1, could restore T-cell immunity. Anti-PD-1/anti-PD-L1 antibodies have demonstrated promising efficacy in the treatment of cancer patients. The toxicity spectrum of PD-1/PD-L1 blockades is distinct from chemotherapy or other target agents. Pneumonitis is one of the major side effects of these drugs, and reported incidences vary substantially between clinical trials. We tried to investigate the overall incidence and risk of treatment-related pneumonitis with anti-PD-1/PD-L1 blockades in cancer patients. Methods: A systematic search of literature up to January 2016 was performed in EMLINE, EMBASE, and Cochrane databases to identify relevant clinical trials. Paired reviewers independently selected articles for inclusion and extracted data. Incidence and relative risk (RR) of hypertension were calculated using a random-effects or fixed-effects model, depending on the heterogeneity of the included studies. Results: A total of 23 clinical trials with 5333 patients were included. The overall incidence of all- and high-grade pneumonitis in cancer patients receiving anti-PD-1/PD-L1 therapies was 3.5% (95% CI, 2.9% to 4.3%) and 1.3% (95% CI, 1.1% to 1.9%), respectively. Anti-PD-1/PD-L1 antibodies were associated with a significantly increased risk of all-grade pneumonitis in patients with cancer with an RR of 5.47 (95% CI, 2.17 to 13.81; P=0.001) compared with controls. The risk of high-grade pneumonitis was also increased with the use of anti-PD-1/PD-L1 antibodies, though not statistically significant (RR 3.86; 95% CI 1.08 to 15.22; p=0.054). Conclusion: Patients with cancer receiving anti-PD-1/PD-L1 therapies have a significant risk of developing pneumonitis. Early and appropriate management is strongly recommended to avoid unnecessary dose reductions and transitory or definitive treatment discontinuations due to pneumonitis.

Keywords: pneumonitis, PD-1, PD-L1, Cancer

OA21: PALLIATIVE AND SUPPORTIVE CARE FOR LUNG CANCER PATIENTS
WEDNESDAY, DECEMBER 7, 2016 - 11:00-12:30

OA21.02 ALK-REARRANGED NON-SMALL CELL LUNG CANCER IS ASSOCIATED WITH A HIGH RATE OF VENOUS THROMBOEMBOLISM
S165

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Abstracts

OA21.05 WET M1A NON-SMALL CELL LUNG CANCER: IS IT POSSIBLE TO PREDICT RECURRENCE OF PLEURAL EUPHUSION?
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Background: Pleural and oncological treatment options for malignant pleural effusion (MPE) are increasing and hence, more accurate prognosis at presentation may help to identify patients with the higher risk of pleural recurrence, in order to individualize more intensive treatment strategies. The aim of this study was to identify predictors of malignant pleural effusion recurrence in patients with M1A non-small cell lung cancer (NSCLC)

Methods: All patients with NSCLC and MPE submitted to pleural palliative procedures including simple pleural drainage, videothoracoscopic pleural drainage, pleurodesis and indwelling pleural catheter were enrolled in a prospective study between 2014 and 2015, and divided into two groups. Group I included patients who had pleural recurrence, and Group II with no pleural recurrence after the palliative procedures. Prognostic factors for pleural recurrence were identified by univariate analysis, using Fisher’s exact test for the analysis of categorical variables and Student’s t test for quantitative variables.

Conclusion: Subsequently the significant variables were entered into a multivariate logistic regression analysis (with p < 0.05 considered significant). The cutoff points for any significant continuous variables were determined by receiver operating characteristics (ROC) analysis. Results: A total of 82 patients were included in the analysis. Median and not time-to-event survival (months) were 10 (range 1 to 1070 days). There were 15 patients (18.3%) in Group I and 67 patients (81.7%) in Group II. Univariate analysis of factors affecting postoperative recurrence were: adenosine deaminase concentration in pleural fluid < 16 mg/dl (p = 0.04), albumin concentration in pleural fluid < 2.4 mg/dl (p = 0.03), administration of second-line palliative chemotherapy (p = 0.018) and type of procedure (simple pleural drainage vs. videothoracoscopic pleural drainage, pleurodesis and indwelling pleural catheter) (p = 0.023). At the multivariate analysis, only the type of procedure (simple pleural drainage) (p = 0.031) was identified as an independent predictor of recurrence.

Conclusion: In our cohort of NSCLC patients with MPE submitted to pleural palliative procedures, simple pleural drainage was the only significantly factor associated with recurrence of MPE. The identification of this factor may assist the choice of the optimal palliative technique, at the first episode of MPE in NSCLC patients. Definitive procedure as pleurodesis is recommended, the indwelling pleural catheter or videothoracoscopic drainage are options for patients whom lung are trapped.

Keywords: Carcinoma, Non-Small-Cell Lung, palliative care, recurrence

OA21: PALLIATIVE AND SUPPORTIVE CARE FOR LUNG CANCER PATIENTS 
WEDNESDAY, DECEMBER 7, 2016: 11:00-12:30

OA21.03 UNMET NEEDS IN PHYSICAL AND EMOTIONAL SIDE EFFECTS DURING LUNG CANCER TREATMENT AND SURVIVORSHIP
Jennifer King, Jamal Bankhead, Maureen Rigney

Background: Previous research has shown that supportive care needs in lung cancer patients are high and that this population may have significantly more unmet care needs than other cancer patients. Our goals for this study were to determine the most prevalent and problematic side-effects of lung cancer and lung cancer treatment in our community and to understand where both patients and caregivers felt there were unmet needs.

Methods: A Community Needs Assessment survey was distributed to lung cancer patients and caregivers electronically between 11/9/2015 and 2/18/2016. 820 people responded, including 477 patients/survivors and 343 caregivers, 181 of whom identified as the primary caregiver. The overall completion rate was 72.6%, similar for both groups. Respondents identified all side effects they or their loved one experienced during and after treatment, as well as 5+ years after diagnosis. They also indicated which of these side-effects were most problematic during those time periods. Respondents were also for demographic information and for open-ended responses about their unmet needs during care and follow-up.

Results: Respondents indicated a high rate of side effects, with over 95% reporting at least one. Importantly, both patients and caregivers reported that physical side effects were significantly more problematic during treatment but that emotional side effects were more problematic after treatment and in the long-term. Patients rated anxiety, fatigue, and shortness of breath as the most problematic short and long-term post-treatment side effects, with 18.29% of patients indicating these items at a particular time period. During treatment, gastrointestinal issues including constipation (18%), diarrhea (17%), and nausea (14%) were also identified as highly problematic side effects by the patients. Caregivers reported similar effects but also rated pain as problematic across all time periods (15-24%) and identified loss of appetite (28%) and weight loss (25%) during treatment. When questioned about unmet needs during treatment and survivorship, respondents frequently commented that their treatment was focused on treatments and survival and not on managing side effects.

Conclusion: Side effect management is a clear unmet need for lung cancer patients and to help support their caregivers. Our data show high levels of emotional and physical side effects and a perceived lack of support for proper management. Notably, emotional side effects are prevalent after treatment for lung cancer into long-term survivorship and are frequently cited as the most problematic issue for those no longer in active treatment.

Keywords: supportive care, side effects, survivorship, lung cancer

OA21: PALLIATIVE AND SUPPORTIVE CARE FOR LUNG CANCER PATIENTS 
WEDNESDAY, DECEMBER 7, 2016: 11:00-12:30

OA21.06 TURNING BEST SUPPORTIVE CARE INTO ACTIVE CARE. A

Keywords: Carcinoma, Non-Small-Cell Lung, palliative care, recurrence

OA22: PALLIATIVE AND SUPPORTIVE CARE FOR LUNG CANCER PATIENTS 
WEDNESDAY, DECEMBER 7, 2016: 11:00-12:30
SESSION OA22: NOVEL TRIALS AND BIOMARKERS IN MPM
WEDNESDAY, DECEMBER 7, 2016 - 14:15-15:45

OA22.01 STELLAR - INTERIM RESULTS OF A PHASE 2 TRIAL OF TTFIELDS WITH CHEMOTHERAPY FOR FIRST LINE TREATMENT OF MALIGNANT MESOTHELIOMA

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Background: Tumor Treating Fields (TTFields) are an anti-mitotic, regional treatment modality, based on low intensity alternating electric fields delivered non-invasively using a portable, home use, medical device. In-vitro, human mesothelioma cells were found to be highly susceptible to TTFields. TTFields have been shown to extend survival of patients with glioblastoma when added to standard of care chemotherapy. Methods: The trial will accrue a total of 80 patients with untreated, previously untreated mesothelioma. Patients are treated with TTFields in combination with peri-maintenance and cisplatin or carboplatin. Continuous TTFields at 240 µW/cm² for a maximum of 18 hours/day began at the thorax tumor with standard dosing of chemotherapy. Inclusion criteria include ECOG 0-1, pathological evidence mesothelioma and at least one measurable lesion according to modified RECIST criteria. Patients are followed q3 weeks (CT scan q6 weeks) until disease progression. The primary endpoint is overall survival (OS). Secondary endpoints are response rate, progression free survival (PFS) and treatment-emergent toxicity. This prospective, single arm study assumes that historical control has an exponential survival distribution and a median survival of 12.1 months (Vogelzang et al.). The sample size provides 80% power with a two sided alpha of 0.05 to detect a Hazard Ratio of 0.67 for OS compared to the historical data. Results: To date, 42 patients were enrolled in the trial with an average follow up time of 11.5 months. Median age is 67.5 (range 43-78), 78% are male and 48% smokers. 14% (6 patients) have metastatic disease and 33% (14 patients) have an ECOG score of 1. Median survival has not been reached at this time. The 12-month survival rate is 79.7% (95% CI 72.9-91.2) and median PFS is 7.3 months (95% CI 5.6-NA). No device-related serious adverse events (AEs) have been reported to date. Expected TTFields-related dermatitis was reported in 55% (23 patients). Only 2 patients had grade 3 dermatitis. The following severe (grade 3-4) systemic AEs were reported: hematological (28%), hepatobiliary (2%), respiratory (2%). Conclusion: These interim results of the ongoing STELLAR study demonstrated no safety concerns for the combination of TTFields to the thorax together with standard chemotherapy for previously untreated mesothelioma patients. The 12-month survival rate was significantly higher, and PFS longer, than that of historical controls reported by Vogelzang et al. Final analysis of the study will be performed after enrollment and follow up of all 80 patients in the study are completed.

Keywords: TTFields, Tumor Treating Fields, mesothelioma, STELLAR

OA22.02 NINTEDANIB PLUS PEMETREXED/CISPLATIN IN PATIENTS WITH MPM: PHASE II FINDINGS FROM THE PLACEBO-CONTROLLED LUME-MESO TRIAL

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Background: Standard first-line treatment for patients with unresectable malignant pleural mesothelioma (PM-M) is pemetrexed/cisplatin, yielding a median overall survival (OS) of only ~1 year, thus new approaches are required. As demonstrated by the bevacizumab MAPS study, inhibition of the VEGF pathway is of interest as a treatment approach for MPM. Nintedanib is an oral, triple angiokinase inhibitor of VEGFR, PDGFR and FGFR. This study will evaluate the efficacy and safety of nintedanib plus pemetrexed/cisplatin in patients with advanced MPM. Methods: Patients with unresectable MPM (chemo-naïve, ECOG PS 0–1) were stratified by histology (epithelioid/biphasic) and randomised (1:1) to receive up to 6 cycles of pemetrexed (500 mg/m²)/cisplatin (75 mg/m²) on Day 1 plus nintedanib (200 mg bid) on Days 2–21. Patients without disease progression received maintenance treatment with nintedanib/placebo. The primary endpoint was progression free survival (PFS). Results: 87 patients were randomised to receive pemetrexed/cisplatin, plus nintedanib/placebo. Patient characteristics were comparable between the groups. PFS was longer in the nintedanib vs the placebo arm, in both the overall study population and in epithelioid patients (Table 1). Preliminary OS data favours nintedanib. No significant treatment associated adverse events (AE, any grade), with 7% of patients in the nintedanib arm discontinuing due to AEs, vs 15% with placebo. Serious AEs occurred in 36% vs 42% of patients in the nintedanib and placebo arms, respectively. The most common grade 3 AE occurring in nintedanib vs placebo patients were neutropenia (34% vs 10%), ALT increase (14% vs 2%) and gamma glutamyltransferase increase (14% vs 0%). Conclusion: Nintedanib plus pemetrexed/cisplatin demonstrated clinical efficacy with improved PFS and a tolerable safety profile in patients with unresectable MPM. Based on these promising findings, this Phase II study was extended to a confirmatory Phase III trial, which is currently enrolling patients. Clinical trial identifier: NCT01907100.
Keywords: malignant pleural mesothelioma, phase II, angiogenesis, antiangiogenesis

OA22.03 HMGB1, A TARGET FOR MESOTHELIOMA THERAPY AND A BIOMARKER TO DETECT ASBESTOS EXPOSURE AND TO IDENTIFY MESOTHELIOMA PATIENTS
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Background: Millions of people have been potentially exposed to asbestos, the primary cause of malignant mesothelioma (MM). Presently, no reliable biomarkers are available to identify among potentially exposed people, those individuals who have actually been exposed and who are at high risk of MM. High Mobility Group Box Protein 1 (HMGB1) is a key mediator of asbestos-induced inflammation and MM pathogenesis. Recently, HMGB1 hyper-acetylation has been functionally associated to its active release by inflammatory cells. Here, we compared the serum levels of total and hyper-acetylated HMGB1 in individuals exposed to asbestos, MM patients and healthy unexposed controls. Methods: We compared the serum levels of total and hyper-acetylated HMGB1 in individuals professionally exposed to asbestos, MM patients and healthy unexposed controls. Previously proposed MM biomarkers fibulin-3, osteopontin, and mesothelin were also blindly measured in blood collected from participants to the study. Results: HMGB1 serum levels reliably distinguished asbestos-exposed individuals and MM patients from unexposed controls. Moreover, the levels of total and hyper-acetylated HMGB1 were significantly higher in MM patients compared to asbestos-exposed individuals, and did not vary with tumor stage, suggesting that early lesions are also associated to increased HMGB1 levels. At a cutoff value of 2.00 ng/mL, the sensitivity and specificity of hyper-acetylated HMGB1 to discriminate MM patients from asbestos-exposed individuals was 100%, outperforming, in parallel experiments, other previously proposed biomarkers: osteopontin, fibulin-3, and mesothelin. When comparing patients with non-MM cytologically benign or malignant pleural effusion, the combination of two biomarkers, HMGB1 and fibulin-3, provided the highest sensitivity and specificity in differentiating these two groups. Moreover, we found that HMGB1 drives MM cell development and sustains MM progression, and we demonstrated that targeting HMGB1 inhibits MM cell growth and motility in vitro, reduced tumor growth in vivo and prolonged survival. Conclusion: Despite the relatively small size of our cohorts, our results are of exceptional significance and clinical relevance as they provide the first biomarker of asbestos exposure and indicate that hyper-acetylated HMGB1 is a very sensitive and specific biomarker to differentiate MM patients from individuals occupationally exposed to asbestos and unexposed controls. Moreover, our results on HMGB1 inhibitors indicate that HMGB1 targeting hampers the malignant phenotype of MM, offering a novel potential therapeutic approach to patients afflicted with this dismal disease.

Keywords: biomarker, HMGB1, Mesothelioma, asbestos

OA22.05 BREATH ANALYSIS BY GAS CHROMATOGRAPHY-MASS SPECTROMETRY CAN BE USED TO SCREEN FOR PLEURAL MESOTHELIOMA
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Background: Malignant pleural mesothelioma (MPM) is an asbestos-related tumour with poor prognosis. Since MPM is diagnosed at advanced stage due to non-specific symptoms and investigations, it is thought that only an early diagnosis will improve patient’s outcome. Breathomics allows to detect volatile organic compounds (VOCs) in breath which can be used as non-invasive biomarkers. Although we were able to discriminate MPM patients from controls using ion mobility spectrometry breathomics, we were not able to identify specific VOCs. Therefore, we aimed to identify VOCs in the breath of MPM persons and persons at risk with gas chromatography-mass spectrometry (GC-MS). Methods: Fourteen MPM patients, eighteen asymptomatic asbestos-exposed individuals, 16 individuals with benign asbestos-related diseases and fourteen healthy non-exposed persons were included. After 2 hours of fasting, participants breathed tidally for 5 minutes through a mouthpiece connected to a VOC filter. Subsequently, a full 50 mL capacity was captured in a Tedlar bag of which 500 mL was immediately transferred on a Tenax®-column. Samples were thermally desorbed followed by GC-MS analysis (Agilent 6890A-Thermos Focus DSQII). VOCs were manually selected in the chromatogram and standardised to an internal standard of n-butanol. Only VOCs with a GC retention time of 4-20 min were used. Using a database of VOCs, significant differences were searched and ROC-curves for discriminating MPM from all control groups were constructed. VOCs which had an AUC of >0.80 were reported. Results: 114 VOCs were selected of which 17 were significantly different between MPM patients and controls. Of these, 7 had AUCs >0.80 and are possible markers for MPM diagnosis.

Conclusion: The large discriminative power and good sensitivity and specificity imply the possibility to use breath analysis for MPM screening. Therefore, persons exposed to asbestos with a positive test should be followed-up in a cost-effective way, decreasing the need for CT-scans and radiation exposure in low-risk persons. Further work includes combining models for discrimination and validating these findings.

Keywords: Mesothelioma, biomarker, breath analysis, volatile organic compounds

OA22.06 REFINEMENT OF THE PROGNOSTIC MIR-SCORE FOR USE IN DIAGNOSTIC SPECIMENS FROM CHEMO-NAÏVE MALIGNANT PLEURAL MESOTHELIOMA PATIENTS
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Background: A 6-microRNA signature (mir-Score, Kirschner et al 2015) was previously demonstrated to show high prognostic accuracy in a series of surgical specimens (with and without induction chemotherapy). In the present study we investigated these microRNAs in an independent cohort of MPM patients all treated with induction chemotherapy following standardized extrapleural pneumonectomy (EPP). The main focus of the study was to evaluate the possible effects of induction chemotherapy on microRNA expression and to refine and validate the mir-Score for use in chemo-naïve diagnostic specimens. Methods: We identified a cohort of 20 MPM patients who received chemotherapy following EPP between 1999 and 2014 at University Hospital Zurich. At present microRNA analysis (RT-qPCR) has been carried out in 34 pairs of chemo-naïve (diagnostic biopsy) and chemotherapy-treated (EPP) specimens. Paired-samples t-test was employed to determine differences in microRNA expression pre- and post-chemotherapy. Accuracy of the mir-Score in predicting a good prognosis (>20 months survival post-surgery) was evaluated by ROC curve analysis. In addition, binary logistic regression modelling was used to build a refined mir-Score. Results: Applying the mir-Score to chemo-naïve diagnostic specimens revealed an area under the ROC curve (AUC) of 0.65 (95% CI: 0.46-0.84), and the same analysis on the EPP specimens gave an AUC of 0.57 (95% CI: 0.37-0.77). Therefore, the accuracy of the mir-Score was lower than observed in the previous study. However, pairwise comparison of microRNA expression before and after chemotherapy showed that although not reaching statistical significance, the levels of several microRNAs were lower following induction chemotherapy. We next employed binary logistic regression modelling on microRNA levels in chemo-naïve tissue to determine whether a refined microRNA signature less susceptible to chemotherapy-induced changes could be created. A refined mir-Score consisting of miR-221 and miR-30e, the two microRNAs least susceptible to chemotherapy, achieved AUCs of 0.77 (95% CI: 0.61-0.94) and 0.80 (95% CI: 0.64-0.96) in diagnostic and EPP specimens, respectively. When applied to samples from the previous study, the refined score resulted in an AUC of 0.72 (95% CI: 0.54-0.90). Conclusion: This validation and refinement
study has shown that the expression of several miR-Score microRNAs appears to be affected by standard chemotherapy. A refined miR-Score was generated which is less susceptible to the effect of chemotherapy and may have prognostic value when applied to diagnostic specimens. Further validation in additional paired samples and investigation of the effect of cisplatin, pemetrexed and gemcitabine on microRNA expression are ongoing.

Keywords: malignant mesothelioma, microRNA, Prognosis

OA22. NOVEL TRIALS AND BIOMARKERS IN MMM
WEDNESDAY, DECEMBER 7, 2016 - 14:15-15:45

OA22.07 CORRELATION OF CT SCAN BASED TUMOR VOLUME MEASUREMENT TO ACTUAL RESECTED TUMOR VOLUME - A NEW T-FACTOR?
Olivia Lau1, Martina Fries1, Thi Dan Linh Nguyen-Kim2, Thomas Frauenfelder2, Sven Hillinger1, Burkhardt Seifert1, Ilhan Incl1, Walter Weder1, Isabelle Opitz1
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Background: Tumor volume has been reported to be a valuable prognosticator for malignant pleural mesothelioma (MPM) survival. We wanted to assess the precision of CT scan based preoperatively measured tumor volume when correlated to the actual resected tumor weight and tumor volume after pleurectomy/decortication. Methods: From 10/2012 – 06/2016 the tumor weight of surgery specimens was measured in 32 patients undergoing macroscopic complete resection by (extended) pleurectomy/decortication (ie P/D). The median tumor weight of all patients was (n=32) 443g (95-783g). In all patients tumor volume was measured in the CT or PET-CT scans performed before surgery as described previously (Frauenfelder 2011). Tumor volume of the resected specimen was additionally measured in 21 patients. Relations between tumor weight, tumor volume at surgery, CT-volume, CT stage and pT stage were analyzed using Spearman rank correlation. Results: Median time between CT scan and surgery was 18 days (range 1-48). The analysis revealed a moderate correlation between CT tumor volume and weight (r=0.001), correlation coefficient 0.58. CT volume and tumor volume at surgery showed strong correlation (p=0.001, correlation coefficient 0.65). No significant correlation was observed between CT stage and tumor weight (p=0.1, correlation coefficient 0.31), but a moderate correlation between CT stage and CT volume (p=0.001, correlation coefficient 0.58) as well as specimen volume (p=0.008, correlation coefficient 0.58). There was a moderate correlation of tumor weight with pT stage (p=0.02, correlation coefficient 0.42), but no correlation of CT volume (p=0.1, correlation coefficient 0.31) as well as specimen volume with the pT stage (p=0.2, correlation coefficient 0.32).

Conclusion: The correlation between preoperatively assessed CT tumor volume and volume of the resected specimen showed a strong correlation. To assess the prognostic role of CT measured tumor volume a correlation to prognosis has to be performed before implementation as a new T-factor.

Keywords: Tumor weight, Tumor volume, Mesothelioma, TNM staging

SESSION OA23: EGFR TARGETED THERAPIES IN ADVANCED NSCLC
WEDNESDAY, DECEMBER 7, 2016 - 14:15-15:45

OA23.01 ANTI-EGFR MONOCLONAL ANTIBODIES PLUS CHEMOTHERAPY IN THE FIRST-LINE TREATMENT OF ADVANCED NSCLC: A META-ANALYSIS
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Background: Monoclonal Antibodies (mAbs) against the Epidermal Growth Factor Receptor (EGFR) in association with platinum-based doublet chemotherapy have emerged as a potential first-line treatment option for advanced non-small cell lung cancer (NSCLC). This study was conducted to systematically review available data and evaluate the efficacy and toxicity of anti-EGFR mAbs plus chemotherapy versus chemotherapy alone for advanced NSCLC. Methods: We carried out a search on network databases and oncology conference abstracts for studies between 1990 and January 2016. Only prospective randomized clinical trials were included. Primary endpoints were overall survival (OS) and toxicity frequency. Secondary endpoints were progression-free survival (PFS) and overall response rate (ORR). Subgroup analysis was performed assessing histological subtypes, EGFR protein expression by immunohistochemistry (IHC), EGFR gene copy number by fluorescence in-situ hybridization (FISH), EGFR mutation status, and smoking status. Results: Seven studies (2 with nectumabum and 5 with cetuximab) were included with 1,055 patients. Compared to chemotherapy alone, significant benefits were demonstrated by the addition of anti-EGFR mAb to chemotherapy in OS (HR 0.90; 95%CI 0.84-0.95), PFS (HR 0.93; 95%CI 0.87-0.98), and ORR (OR 1.27; 95%CI 0.66-2.05). In subgroup analyses, the association of anti-EGFR mAbs was associated with improved OS among patients with squamous histology (HR 0.84; 95%CI 0.70-0.92), tumours with high EGFR expression by IHC (HR 0.83; 95%CI 0.70-0.98), and smokers (HR 0.87; 95%CI 0.70-0.96). Patients with squamous histology and high EGFR expression by IHC achieved the highest benefit with the association (HR 0.71; 95%CI 0.58-0.86). The OS with the association also seemed to be higher in EGFR FISH negative and in EGFR wild-type tumours, but without statistical significance. Chemotherapy plus anti-EGFR mAb caused more grade 3 or worse adverse events (OR 1.73; 95%CI 1.50-2.00) especially these known to be associated with anti-EGFR therapy, such as acne-like rash (OR 34.13; 95%CI 16.60-71.00) and hypomagnesemia (OR 6.23; 95%CI 3.04-12.77). Conclusion: Anti-EGFR therapy plus platinum-based doublet chemotherapy as first-line treatment demonstrated significant efficacy benefits with acceptable toxicity for advanced NSCLC. This benefit is more expressive among squamous histology with high EGFR expression. EGFR protein expression by IHC seems to be a predictive marker for survival in the association group. Further research is needed to corroborate these findings.

Keywords: anti-EGFR, biomarker, Targeted therapy, Individual Medicine

OA23.02 EFFICACY AND SAFETY OF NECTUMABUM CONTINUATION MONOTHERAPY IN PATIENTS WITH EGFR-EXPRESSING TUMORS IN SQUIRE, A PHASE 3 STUDY
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Background: SQUIRE (NCT00981058) demonstrated adding necitumabum (N) to gemcitabine/cisplatin (GC) improved survival in patients with Stage IV squamous NSCLC (SQ-NSCLC). Retrospective analysis revealed consistent treatment benefit in favor of patients receiving N monotherapy as continuation after chemotherum (CT) (GC-N continuation patients versus continuation therapy eligible GC arms patients) (GC non-progressors). In the EU, N is approved for patients with EGFR-expressing tumors. We repeated the analysis in this patient population. Methods: Patients with Stage IV SQ-NSCLC were randomized 1:1 for 6 cycles of G (1250 mg/m2 iv, Days [d] 1,8) and C (75 mg/m2 iv, d) either with or without N (800 mg iv, d1). Patients in GC+N without progression continued N until progressive disease (PD). SQUIRE included mandatory tissue collection. EGFR protein expression was assessed by IHC in a central lab (Dako EGFR PharmDx kit). Analyses were done in EGFR-expressing patients (EGFR +).  Patients who received ≥4 cycles of CT
without PD were included. Overall survival (OS) and progression-free survival (PFS) were calculated by Kaplan-Meier method. 95% Cls and hazard ratios estimated using stratified Cox proportional hazards model. Results: Of 1093 patients (population), 982 patients (98.9%) had evaluable IHC assay results. Of 982 patients, 228 patients (23.0%) had EGFR expression determined by immunohistochemistry. Pre-treatment serum samples were analyzed with VeriStrat®, a MALDI-TOF mass spectrometry test, and classified as VeriStrat-Good or VeriStrat-Poor-risk. Results: 15/338 patients treated with afatinib were long-term responders. Median duration of treatment was 16.6 months (range: 12.3-25.8). Patient characteristics were similar to the overall dataset (median age: 65 years (range: 54-81); male: 80.0%; Asian: 13.3%; ECOG 0/1: 40.0%/60.0%; best response to chemotherapy CR or PR/SD: 53.3%/46.7%; current and ex-smokers: 80.0%). Median PFS was 16.2 months (range: 2.8-24.0); median OS was 23.1 months (range: 12.9-31.5). The most common treatment-related AEs (all grade/grade 3) were diarrhea (73.3%/67.0%), rash/acne (66.7%/67.0%); stomatitis (13%/17%). AEs generally occurred soon after treatment onset (median onset, days: diarrhea 11 [5-48]; rash/acne 17 [9-107]; stomatitis 15 [11-91]). Four patients required a dose reduction to 30mg/day due to treatment-related AEs (diarrhea, rash, stomatitis, diarrhea/ rash). OS was undertaken in 4 patients. Genomic aberrations in the ErbB/FGF gene families were identified in 44.4%/55.6% of long-term responders (overall dataset: 29.4%/58.0%). Of 14 patients assessed by VeriStrat, 85.7% were VeriStrat-Good (overall dataset: 61.6%). Immunohistochemistry data was available for two patients; one overexpressed EGFR (20% positive cells; H-score ≥200) Conclusion: Baseline characteristics of long-term responders to afatinib were similar to the overall dataset. In this sub-group, afatinib conferred a survival benefit of nearly 2 years. Afatinib was well tolerated with predictable and transient AEs that occurred soon after treatment. The dataset was too small to identify any clear NGS/VeriStrat predictive signals. Further studies are required to predict long-term response to afatinib.

Keywords: afatinib, Squamous cell carcinoma of the lung, NSCLC

OA23.05 FIRST-LINE AFATINIB VERSUS GEFITINIB IN EGFRM+ ADVANCED NSCLC: UPDATED OVERALL SURVIVAL ANALYSIS OF LUX-LUNG 7 Keunchil Park1, Eng Huat Tan1, Li Zhang1, Vera Hirsh2, Ken O’Byrne3, Michael Boyer1, James Chih-Hsin Yang1, Tony Mok1, Ki Hyeong Lee1, Shun Lu2, Yuankai Shi3, Sang We Kim4, Jannesa Laskin4, Dong Wan Kim4, Scott Launie1, Karl Kolbeck1, Jean Fan5, Nigel Dow6, Pasi Aaltomaa6, Gabriella Herodek7, Vassilis Georgoulias8, Nicholas Dupuis9, Claudia Bühnemann10, Andrea Ardizzoni11, Andrea Ardidzoni11, Enrique Filip12, Shrish Gadgeil13, Vassilis Georgoulias8, Nicholas Dupuis9, Claudia Bühnemann10, Neil Gibson14, Eva Ehrnrooth15, Jean-Charles Soría16, Nicholas Dupuis9, Boehringer Ingelheim Corporation, Ridgefield/CO/United States of America, 1Department of Medical Oncology, University of Otago, Otago/ON/New Zealand, 2Department of Medical Oncology, Hospital Universitario Doce de Octubre and Cnio, Madrid/Spain, 3Boehringer Ingelheim, Squamous cell carcinoma of the lung, NSCLC

Introduction: Afatinib and gefitinib are both approved by the US FDA for first-line treatment of patients with advanced NSCLC. This Phase IIb trial prospectively compared afatinib versus gefitinib in this setting. Methods: LUX-Lung 7 assessed afatinib (40 mg/day) versus gefitinib (250 mg/day) in treatment-naive patients with stage IIIB/IV NSCLC harbouring a common EGFR mutation (Del19/L858R). Co-primary endpoints were PFS (independent review) and treatment duration. As per protocol, OS endpoints included ORR and AEs. In case of grade ≥3 selected grade 2 drug-related AEs the afatinib dose could be reduced to 30 mg or 20 mg (minimum). The primary analysis of PFS/TTF was undertaken after −250 PFS events. The primary OS analysis was planned after −213 OS events and a follow-up period of ≥32 months. Results: A total of 319 patients were randomized 1:1 to afatinib (n=159) or gefitinib (n=160); gefitinib: 159). At the time of primary analysis, PFS (HR (95% CI): 0.73 [0.57-0.95], p=0.017), TTF (0.73 [0.58-0.92], p=0.007) and ORR (70 vs 56%, p=0.008) were significantly improved with afatinib versus gefitinib. The most common treatment-related AEs were diarrhoea (13%) and rash/ acne (9%) with afatinib and elevated ALT/AST (9%) with gefitinib. 24% of patients treated with afatinib had ≥1 dose reduction due to AEs; dose reductions were more common in
females than males (77%/23%) and non-Asians than Asians (64%/36%). Dose reduction of afatinib did not negatively impact PFS (<40mg vs >40mg; HR [95% CI]: 1.34 [0.90-2.00]) but reduced incidence and severity of drug-related grade ≥3 AEs. Treatment discontinuation due to drug-related AEs was the same in each arm (6%). The data cut-off for primary OS analysis occurred on 8 April 2016. At this time, median treatment duration (range) was 13.7 (0-46.4) versus 11.5 (0.5-48.7) months with afatinib and gefitinib. 25% (afatinib) and 13% (gefitinib) of patients received treatment for ≥24 months. 73% and 77% of patients in the afatinib and gefitinib arms had ≥1 subsequent systemic anti-cancer treatment, with 46% and 56% receiving a subsequent EGFR-TKI including osimertinib (14%)/olmutinib (14%). OS data, including subgroup analysis with respect to subsequent therapy will be presented at this meeting.

Conclusion: Afatinib significantly improved PFS, TTF and ORR versus gefitinib in FFR+m NSCLC patients, with a manageable AE profile and few drug-related discontinuations. Dose adjustment of afatinib reduced drug-related AEs without compromising efficacy. Primary OS analysis will be reported.

Keywords: afatinib, gefitinib, NSCLC, EGFR

OA23. EGFR TARGETED THERAPIES IN ADVANCED NSCLC
WEDNESDAY, DECEMBER 7, 2016: 14:15-15:45

OA23.06 OVERALL SURVIVAL (OS) OF EGFR MUTATION POSITIVE NON- small cell Lung Cancer patients: REAL-WORLD TREATMENT PATTERNS OF 1,660 JAPANESE PATIENTS
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Background: Since the epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) was launched in Japan, the survival periods of advanced/recurring EGFR mutation positive (EGFR m+) non-small cell lung cancer (NSCLC) patients have been getting longer. However, clinical factors which contributed to the extension of survival periods of these patients remain unclear. We investigated overall survival, prognostic factors and treatment patterns of EGFR m+ NSCLC patients in real-world clinical practice. Methods: This is a multi-center, observational, retrospective study. Histologically or cytologically diagnosed EGFR m+ NSCLC patients who were started first-line treatment from 3/2008 to 3/2012 were enrolled. The primary objective was the estimated OS. The secondary objectives were to determine prognostic factors, real-world treatment patterns. Results: 1,660 EGFR m+ NSCLC patients were enrolled from 17 hospitals in Japan (median age 67.0 years, female 64.8%, 38.9% had smoking history, ECOG-performance status 0, 1, 2, 3 were 39.5%, 41.7%, 7.1%, 4.9%, 0.7%, respectively, adenocarcinoma 95.2%, 50.1% exon 19 deletion, 66.7% at stage IV). Median estimated OS was 29.7 months. Cox regression analysis revealed age, smoking history, performance status, histological diagnosis, EGFR mutation type and clinical stage were independently associated with OS. Five year survival rate of stage IV patients was 13.8%. The median number of treatment regimens was two. EGFR-TKI and platinum-doublet chemotherapy were most frequently used as first- and second-line treatments. Conclusion: Real world treatment of the large data-set of 1,660 EGFR m+ NSCLC patients was retrospectively investigated. Median OS was 29.7 months and EGFR-TKIs are major components of the treatment regimens for these patients in Japan. (NCT0247520)

Keywords: NSCLC, Real world, overall survival, EGFR

OA23. EGFR TARGETED THERAPIES IN ADVANCED NSCLC
WEDNESDAY, DECEMBER 7, 2016: 14:15-15:45

OA23.07 ANALYSIS OF OUTCOMES IN US IRessa CLINICAL ACCESS PROGRAM (ICAP) PATIENTS ON GEFTINIB FOR MORE THAN 10 YEARS
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Background: In 2011, following gefitinib (IRESSA®) FDA voluntary withdrawal, US patients benefiting from gefitinib were eligible to continue gefitinib through the IRESSA Clinical Access Program (ICAP), an IRB-approved protocol. A subset of ICAP investigators subsequently collected additional retrospective data on their ICAP patients through another IRB-approved project (“chart-review subset”). Methods: For all enrolled ICAP patients, demographic and serious adverse event (SAE) reports were reviewed. All ICAP investigators were invited to participate in chart review, 47 accepted and collected data on patient/tumor characteristics and safety/tolerability of prolonged gefitinib therapy among their 79 ICAP patients. Results: Across 137 US sites, 191 patients enrolled in ICAP. As of September 2016, 75% (35%) remain on gefitinib; discontinuations were due to progression (36%), death (34%), AE’s (13%), or other (17%). Forty-six (34%) patients reported 162 SAEs; 5 (2.6%) patients had 12 SAEs considered to be gefitinib-related by investigators. The chart-review subset included 79 (41%) patients with median age of 69 years at ICAP enrollment, who were predominantly female (70%) and white (84%); 55% had a confirmed NSCLC diagnosis. Due to the evolving understanding of genetic mutations in NSCLC at the time of gefitinib initiation, the majority of patients (79%) never had EGFR sequencing performed. Although tissue is not available for EGFR status confirmation, we assume these patients are nearly exclusively EGFR mutation-positive. Median total length of gefitinib was 11.1 years (6.5-15.1; Table). Ten-year survival rate from first-ever initiation of gefitinib was 86% and 15-year was 59%. Table. Gefitinib treatment patterns and tolerability among ICAP chart-review patients.

Parameter n, %
Observed Population (N=79)
Median duration, y, range 11.1 (6.5-15.1)
Median duration, y, range 7.8 (5.4-10.9)
Starting dose 250 mg/day 67 (84.8)
No dose changes due to AEs 75 (94.9)
Median duration, y, range 3.5 (0.0-4.7)
Dose: 250 mg/day 76 (96.2)
Treatment-related AEs Grade 1-2 13 (16.5) (11.3) (2.5)
Grade unknown
Dose reductions due to treatment-related AEs 1 (1.3)
Discontinuations due to treatment-related AEs 4 (5.1)
Discontinuations due to progressive disease 11 (28.9)

Conclusion: The majority of this subset of patients who participated in ICAP based on long-term clinical benefit from gefitinib continue to do well with gefitinib, demonstrating good tolerance of therapy and survival for a median duration of more than 10 years.

Keywords: gefitinib, NSCLC, EGFR-TKI, Long-term

SESSION OA24: RADIOTHERAPY OF LUNG CANCER: RECENT DEVELOPMENTS
WEDNESDAY, DECEMBER 7, 2016: 14:15-15:45

OA24.01 RADIOTHERAPY QUALITY ASSURANCE OF CONCURRENT CHEMORADIOTherapy IN PROCLAIM PHASE III TRIAL
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Background: Trials of chemoradiotherapy for different tumors, including lung cancer, have shown a correlation between protocol deviations and adverse outcomes. Radiation quality assurance (RTQA) was mandated for all patients...
treated in the PROCLAIM (NCT00686959) trial evaluating two different chemoradiotherapy regimens. Methods: The study was open to accrual between 2008-2012. Planned chemoradiotherapy dose was 60-66 Gy in daily 2 Gy fractions. Dose was escalated through the review of radiation treatment plans and monitoring of protocol violations. Review of the radiation plan was mandated for all patients; prior to radiation start for the first enrolled patient at each site. Real-time review was performed randomly in 20% of additional patients with non-real-time review performed for the remainder. Parameters assessed for major violations per protocol included: <95% of planned total volume (PTV) received by 93% of prescribed dose; >1 cm² contiguous volume within or outside the PTV received >115% of prescribed dose; $V_{95}$ (volume of lung receiving ≥95 Gy) >38%; and maximum point dose to spinal cord of >48 Gy. Overall survival (OS) and progression-free survival (PFS) were analyzed using Kaplan-Meier methodology and groups were compared by log-rank test and Cox proportional hazard modeling. Results: Of 598 patients randomized in 126 investigational sites, 554 received study assigned chemoradiotherapy. The median dose delivered was 66 Gy, with 92.6% of patients receiving planned chemoradiotherapy dose (60-66 Gy). A total of 40 patients, enrolled at twenty-eight sites had major RTQA violations. Seven sites enrolled ≥2 patients with major violations. Patients with major violations has a higher incidence of Stage IIIB disease (70.0% vs. 50.6%) and larger tumors (median planned PTV=653 vs. 523cc) than patients with no violations. Patients treated at sites with ≥2 patients with violations (n=86), had a lower median OS (median 21.1 vs. 28.8 months; HR 1.442) and median PFS (median 7.3 vs. 11.3 months; HR 1.345) than patients at sites where none had violations. Conclusion: Major chemoradiotherapy protocol violations were uncommon in the PROCLAIM study, which may be a reflection of the mandatory RTQA. Protocol violations were more frequent in patients with Stage IIIB and larger tumors, which generally require more complex chemoradiotherapy plans. The observation of discrepant outcomes at centres with multiple major RTQA violations is hypothesis-generating but should be interpreted with caution due to the small number of patients.

Keywords: pemetrexed, Radiotherapy, quality assurance

Figure 1: (A) Tumor volume delineation at first CT simulation; (B) the reduced target volume at replanning CT Conclusion: The possibility to reduce toxicity and the documented low rate of marginal failures makes the adaptive approach a modern option for future randomized studies. The best scenario to confirm tumor activity is its application in neoadjuvant chemoradiation trials.

Keywords: Locally advanced NSCLC, chemoradiation, adaptive radiotherapy

OA24.03 CARDIAC TOXICITY AFTER RADIATION FOR STAGE III NSCLC: POOLED ANALYSIS OF DOSE-ESCALATION TRIALS DELIVERING 70-90 GY

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Background: Radiation (RT) associated cardiac injury in patients with lung cancer, especially of unclear significance. RTOG 0617 demonstrated reduced overall survival (OS) with dose-escalated RT for Stage III NSCLC, with higher heart doses predicting for worse OS. We assessed the impact of heart doses on toxicity and survival for patients enrolled on several prospective RT dose-escalation trials. Methods: From 1999-2009, 133 patients with Stage III NSCLC (ECOG PS 0-1) were treated on six prospective trials using induction/concurrent chemotherapy and dose-escalated conformal RT to 70-90 Gy. Broad clinical outcomes (e.g. OS) were prospectively assessed. RT plans were reviewed, cardiac structures were defined, and dose/volume metrics were computed. Patient records were retrospectively reviewed for post-RT symptomatic cardiac events (symptomatic pericardial effusion, acute coronary syndrome, and pericarditis). Baseline cardiac risk was calculated using the World Health Organization/International Society of Hypertension (WHO/ISH) score. A competing risks model accounting for the risk of death was used for statistical analysis. Results: 112 patients were included in the final analysis. Median f/u was 19 mo. (75 mo. for the 39 patients without documented progression). Median OS and PFS were 22 and 12 mo. Median prescribed RT dose was 74 Gy. 15 patients (13%) had symptomatic cardiac events (6 pericardial effusion, 5 myocardial infarction, 2 unstable angina, 2 pericarditis) at median 26 mo. post-RT (range, 7-68). On univariate analysis, Heart mean dose (p=0.001), Heart V50Gy (p=0.002), and Heart V30Gy (p=0.002) were associated with symptomatic cardiac events, whereas baseline WHO/ISH score (p=0.204) and coronary artery disease (p=0.109) were not. Heart doses were higher in patients with vs without events (mean 226Gy vs 116Gy, V50Gy 60% vs 35%, V30Gy 35% vs 14%). On multivariate pair analysis accounting for baseline risk, heart doses remained significant predictors of cardiac events (e.g. Heart mean dose, p=0.001), Heart 105Gy (p=0.055). 2-year competing risk-adjusted rate of symptomatic cardiac events was 11.1% vs 1.5% for Heart mean dose >15Gy vs <15Gy (p=0.003, HR 6.7. 34 patients (30%) had coronary revascularization. Conclusions: Clinically significant symptomatic cardiac events occurring high-dose thoracic RT for Stage III NSCLC occurred in 13% of patients at a median 2 years post-RT, with the rate appearing to be heart dose dependent. RT-associated cardiac toxicity is the definitive treatment of Stage III NSCLC may occur earlier than historically understood, and heart doses should be minimized. Supported in part by NIH grant CA69579.

Keywords: radiation heart toxicity, Stage III NSCLC, cardiac, dose escalation

OA24.05 THE NORDIC HILUS-TUMOR - FIRST REPORT OF A PHASE II TRIAL OF SBRT OF CENTRALLY LOCATED LUNG TUMORS

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Background: Early attempts of stereotactic body radiation therapy (SBRT)
of centrally located lung tumors resulted in high toxicity, questioning the utility of the method in this situation. Since then, different risk adapted fractionation schedules with acceptable toxic effects have been reported from various institutions. However, consensus on the tolerability of centrally located structures to high-fraction doses is still lacking and the clinical toxic effects in relation to dose to organs at risk (OAR) need to be evaluated. Methods: We here report a first toxicity analysis of the HILUS-trial – a prospective Nordic multicenter non-randomized phase II trial of SBRT for centrally located lung tumors. Patients with a centrally located tumor (defined as ≤1cm from the proximal bronchial tree) from either a primary non-small cell lung cancer (NSCLC) or a progressive metastasis from another solid tumor were eligible for the trial. Maximum tumor diameter was 5 cm. Patients receiving concomitant systemic anticancer therapy or with tumors reaching through the wall of a main bronchus were not eligible. All the patients were treated with 7 Gy x 8 and stratified to either arm A (=tumors close to a main bronchus) or arm B (=tumors close to a lobar bronchus). The aim was to include 30 patients in each arm. Follow-up was conducted every 3rd month during the first 2 years and thereafter every 6th month. The trial was approved by ethical committees in each country. Results: Seventy-four patients (42 in arm A and 31 in arm B) were included between 2011 and 2016. Sixty-five patients experienced side effects from the study treatment; the most common being grade 1-2 dyspnea, grade 1-2 cough and grade 1-2 fatigue. Twenty-one patients (28%) experienced grade 3-5 side effects (atrioventricular block, bleeding, dyspnea, empyema, fatigue, fever, fistula, lung infection, pain, pneumonitis, pneumothorax and ventricular arrhythmia). Seven patients (6 in group A and 1 in group B) may have suffered grade 5 side effects; six patients experienced lethal hemoptysis after a median of 15.5 months (2.5-21 months) and one patient suffered from a lethal pneumonitis 5 months after study treatment. Grade 4-5 side effects occurred more frequently in group A than in group B (19% vs 3%). Further analyses of risk factors for serious toxicity in relation to dose-volume parameters and patient- and tumor characteristics will be presented. Conclusion: SBRT of centrally located tumors may be afflicted with high risk of serious toxicity and further evaluation of clinical and dose-volume dependent risk factors are highly warranted.

Keywords: side effects, SBRT, stereotactic, central lung tumors

OA24.06 HISTOLOGIC SUBTYPE OF EARLY-STAGE LUNG ADENOCARCINOMA IS A PREDICTOR OF FAILURE PATTERNS AFTER STEREOTACTIC BODY RADIATION THERAPY
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Background: Stereotactic body radiation therapy (SBRT) has emerged as an effective treatment for early-stage lung cancer. Histologic subtyping in surgically resected lung adenocarcinomas is recognized as a prognostic factor, with the presence of solid or micropapillary patterns predicting poor outcomes. Herein, we describe outcomes following SBRT for early-stage lung adenocarcinoma by histologic subtype. Methods: We identified 119 consecutive patients (124 lesions) with stage I-IIA lung adenocarcinoma who were treated with definitive SBRT at our institution between August 2008 and August 2015 and had undergone core biopsy. Histologic subtyping was performed according to the 2015 WHO Classification. Thirty-seven tumors (30%) were of high risk subtype, defined as containing a component of solid and/or micropapillary pattern. Cumulative incidences of local, nodal, regional and distant failure were compared between high risk vs. non-high risk adenocarcinoma subtypes with Gray's test, and multivariable-adjusted hazard ratios were estimated from propensity score-weighted Cox regression models. Results: Median follow-up for the entire cohort was 17 months and 21 months for surviving patients. The 1-year cumulative incidence of local, nodal, regional and distant failure, respectively, in high risk and non-high risk lesions were 7.3%, 14.8%, 4.0%, 22.7% and 2.7%, 2.6%, 1.2%, 3.6%. Hazard ratios for local, nodal, regional and distant failure, respectively, of high risk lesions compared to non-high risk were 16.8 (95% CI 3.5-81.4), 3.8 (95% CI 0.9-15.0), 20.9 (95% CI 2.1-212.3), 6.9 (95% CI 2.1-21.1). No significant difference was seen with regard to overall survival. Conclusion: Outcomes following SBRT for early-stage adenocarcinoma of the lung are highly correlated with histologic subtype, with micropapillary and solid tumors portending significantly higher rates of locoregional and metastatic progression. In this context, histologic subtype based on core biopsies is a novel prognostic factor and may have important implications for patient selection, adjuvant treatment, biopsy methods and clinical trial design.

Keywords: early stage NSCLC, Patterns of failure, SBRT, Adenocarcinoma

OA24.07 THE IMPACT OF POPULATION HETEROGENEITY ON THE EFFICACY OF SBRT TO THE LUNG
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Background: Stereotactic Body Radiation Therapy (SBRT) is the standard of care for medically inoperable patients with early-stage non-small cell lung cancer (NSCLC). However, NSCLC is comprised of several histological subtypes and the impact of this heterogeneity on SBRT treatments has yet to be established. Methods: We analyzed 740 early-stage NSCLC patients treated definitively with SBRT from 2003 through 2015. We calculated cumulative incidence curves using the competing risk method and identified predictors of local failure using Fine and Gray regression. Results: Overall, 72 patients had a local failure with a cumulative incidence of local failure at three years of 11.8%. On univariate analysis, squamous histology, younger age, fewer medical comorbidities, higher BMI, higher PET SUV, central tumors and lower radiation dose were associated with an increased risk of local failure. On multivariable analysis, squamous histology (HR 2.4 p = 0.008) was the strongest predictor of local failure. Patients with squamous cancers fail SBRT at a significantly higher rate than those with adenocarcinomas or NSCLC not otherwise specified, with three-year cumulative incidences of local failure of 18.9% (95% CI 12.7-25.1%), 8.7% (95% CI 4.6-12.8%), 4.1% (95% CI 0-9.6%), respectively. Conclusion: Our results demonstrate an increased rate of local failure after SBRT in patients with squamous cell carcinoma. Standard approaches for radiotherapy that demonstrate efficacy for a population may not achieve optimal results for individual patients. Establishing the differential dose-responses of SBRT across histological groups is likely to improve efficacy and inform ongoing and future studies that aim to expand indications for SBRT.

Keywords: SBRT, Squamous cell carcinoma, precision medicine, local failure
MA00.01 DETECTION OF LUNG CANCER AND EGFR MUTATIONS BY ELECTRONIC NOSE SYSTEM
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1Clalit Health Services, Petach Tiqwa/Israel, 2Department of Chemical Engineering, Russell Berrie Nanotechnology Institute, Technion, Haifa/Israel, 3The Thoracic Cancer Research and Detection Center, Sheba Medical Center, Ramat Gan/Israel, 4Lung Cancer Unit, Sheba Medical Center, Ramat Gan/Israel, 5Thoracic Cancer Unit, Davidoff Cancer Center, Petach Tiqwa/Israel, 6Department of General Thoracic Surgery, Sheba Medical Center, Ramat Gan/Israel

Background: Early detection of LC has been well established as a significant key point for patient survival and prognosis. New sensitive nanoarray sensors for exhaled Volatile Organic Compounds (VOCs) were developed and coupled with powerful statistical programs; diseases such as LC could be suspected.

Methods: Breath samples were taken from patients who were evaluated for pulmonary nodules, LC patients before treatment and other control patients. ‘Breath-prints’ were recognized by nanomaterial based sensor array/Artificial Olfactory System (NaNose)® and Pattern recognition methods were used.

Results: A total of 139 patients participated in this study, 30 patients with benign nodules, 89 LC patients (16 early and 73 advanced disease) and 20 controls. We revealed significant discrimination between all groups with accuracy of 75.6% to 90.9%. Discrimination of LC from benign nodules had accuracy of 75.6% to 90.9%. Discrimination of LC from benign nodules had accuracy of 75.6% to 90.9%. Discrimination of LC from benign nodules had accuracy of 75.6% to 90.9%. Discrimination of LC from benign nodules had accuracy of 75.6% to 90.9%. Discrimination of LC from benign nodules had accuracy of 75.6% to 90.9%

Conclusion: Breath analysis could discriminate LC patients from benign pulmonary nodules and between EGFR positive and negative mutations. In future, a portable, non-expensive, simple and user-friendly device may support evaluation of pulmonary nodules.

Keywords: lung cancer, EGFR mutations, breath analysis, pulmonary nodules

MA01.02 NON-INVASIVE LUCED® TEST FOR ENDOBRONCHIAL DYSPLASIA, ENABLING CHEMOPREVENTION THERAPY WITH DRUGS SUCH AS ILOPROST
Michael Meyer1, Rahul Kattadare1, Chris Presley1, David Wilbur1, David Steinhauser1, Janning Liang1, Javier Zulueta2, Robert Keith1, York Miller1, Wilbur Franklin1, Gregory Yang1, Jon Hayenga1, Alan Nelson1
1Visiaglate, Phoenix/AZ/United States of America, 2Visiaglate, Phoenix/United States of America, 3Visiaglate Consultant, Boston/MA/United States of America, 4Arizona State University, Tempe/AZ/United States of America, 5Pulmonary Medicine, Denver Veteran Affairs Medical Center, Denver/CO/United States of America, 6Pulmonary and Critical Care Medicine, University of Colorado Anschutz Medical Campus, Aurora/CO/United States of America, 7University of Colorado

Background: The LuCED test for early stage lung cancer detects rare abnormal cells that are exfoliated from tumors into sputum and promotes cancer case detection with >92% sensitivity and >95% specificity. Additionally, the LuCED test detects endobronchial lung dysplasia to triage patients with pre-cancer to chemoprevention therapy involving drugs such as lroprost that show potential for reversing dysplasia. This test is complementary to lung cancer screening methods such as LDCT that do not detect dysplasia. We discuss the performance of the LuCED test for the non-invasive detection of endobronchial dysplasia.

Methods: We analyzed 23,188 normal, 690 cancer, and 65 moderate/severe dysplasia cells from patient sputum. Each individual cell was imaged in 3D using the Cell-CT. Cells were analyzed to measure 594 3D cell types.

Results: Areas under ROC curves for the two diagnostic bins were both >0.993. Thresholds were chosen to yield case specificity >95%. Using these thresholds, cell classification sensitivity of 75% was measured for cancer and dysplasia detection. Since abnormal sputum typically contains at least three abnormal cells the cancer case detection sensitivity is at least 100% x [1 – (1 – 0.75)] = 98%.

Conclusion: Breath analysis could discriminate LC patients from benign pulmonary nodules and between EGFR positive and negative mutations. In future, a portable, non-expensive, simple and user-friendly device may support evaluation of pulmonary nodules.

Keywords: lung cancer, EGFR mutations, breath analysis, pulmonary nodules

MA01.03 THE NON-INVASIVE LUCED® TEST FOR DETECTION OF EARLY STAGE LUNG CANCER
Michael Meyer1, Timothy Bell1, Daniel Sussman1, David Wilbur1, Chris Presley1, Jon Hayenga1, Frances Lakers1, Jonas Reyna1, Michael Davies1, John Field1, Gregory Yang2, Christy Lancaster1, Javier Zulueta2, Alan Nelson1
1Visiaglate, Phoenix/AZ/United States of America, 2Visiaglate, Phoenix/United States of America, 3Visiaglate Consultant, Boston/MA/United States of America, 4Molecular and Clinical Care Medicine, University of Liverpool, Liverpool/United Kingdom, 5Cancer Research Centre, University of Liverpool, Liverpool/United Kingdom, 6Yuma Regional Medical Center, Yuma/United States of America

Background: The LuCED test for early stage lung cancer detects rare abnormal cells that are exfoliated from tumors into sputum and promotes cancer case detection with >92% sensitivity and >95% specificity. Additionally, the LuCED test detects endobronchial lung dysplasia to triage patients with pre-cancer to chemoprevention therapy involving drugs such as lroprost that show potential for reversing dysplasia. This test is complementary to lung cancer screening methods such as LDCT that do not detect dysplasia. We discuss the performance of the LuCED test for the non-invasive detection of endobronchial dysplasia.

Methods: We analyzed 23,188 normal, 690 cancer, and 65 moderate/severe dysplasia cells from patient sputum. Each individual cell was imaged in 3D using the Cell-CT. Cells were analyzed to measure 594 3D cell types.

Results: Areas under ROC curves for the two diagnostic bins were both >0.993. Thresholds were chosen to yield case specificity >95%. Using these thresholds, cell classification sensitivity of 75% was measured for cancer and dysplasia detection. Since abnormal sputum typically contains at least three abnormal cells the cancer case detection sensitivity is at least 100% x [1 – (1 – 0.75)] = 98%.

Conclusion: Breath analysis could discriminate LC patients from benign pulmonary nodules and between EGFR positive and negative mutations. In future, a portable, non-expensive, simple and user-friendly device may support evaluation of pulmonary nodules.

Keywords: lung cancer, EGFR mutations, breath analysis, pulmonary nodules
Background: LDCT screening for lung cancer often triggers follow-up scans for indeterminate nodules. The non-invasive LuCED test for detection of early stage lung cancer may resolve nodule findings and reduce LDCT false positives. In LuCED, patient sputum is analyzed by the Cell-CT® which computes 3D images of single cells allowing measurement of 3D structural biomarkers to identify potential abnormal cells. Final case disposition is determined through cytology review of these cells. Example images of abnormal cells identified by LuCED are shown in the figure.

Methods: Sputum samples from 127 patients were processed by LuCED: 65 patients had biopsy-confirmed lung cancer, and 62 patients were normal controls. Sensitivity was computed as the percentage of cancer cases where abnormal cells were found by LuCED. Generally, abnormal cells found in a case otherwise understood to be normal could constitute a diagnostic overcall and counted as a false positive. However, a finding of abundant (1) otherwise understood to be normal could constitute a diagnostic overcall and counted as a false positive. However, a finding of abnormal cells were found by LuCED. Abnormal cells were found in 61 of 65 cancer cases for controls. Sensitivity was computed as the percentage of cancer cases where abnormal cells were found by LuCED. Generally, abnormal cells found in a case otherwise understood to be normal could constitute a diagnostic overcall and counted as a false positive. However, a finding of abnormal cells were found by LuCED. Abnormal cells were found in 61 of 65 cancer cases for controls. Sensitivity was computed as the percentage of cancer cases where abnormal cells were found by LuCED. Generally, abnormal cells found in a case otherwise understood to be normal could constitute a diagnostic overcall and counted as a false positive. However, a finding of abnormal cells were found by LuCED. Abnormal cells were found in 61 of 65 cancer cases for controls. Sensitivity was computed as the percentage of cancer cases where abnormal cells were found by LuCED. Generally, abnormal cells found in a case otherwise understood to be normal could constitute a diagnostic overcall and counted as a false positive.

Results: In LuCED, patient sputum is analyzed by the Cell-CT® which computes 3D images of single cells allowing measurement of 3D structural biomarkers to identify potential abnormal cells. Final case disposition is determined through cytology review of these cells. Example images of abnormal cells identified by LuCED are shown in the figure.

Keywords: Suspicious nodules may be efficiently reconciled by LuCED when used of detecting pre-cancerous conditions of the lung. Results suggest that demonstrates accurate detection of early stage lung cancer with the potential leading to specificity of 96.7% (N = 61).

Conclusion: The LuCED test demonstrates accurate detection of early stage lung cancer with the potential of detecting pre-cancerous conditions of the lung. Results suggest that suspicious nodules may be efficiently reconciled by LuCED when used adjunctively with LDCT.

Keywords: Indeterminate nodules, LuCED, Non-Invasive, LDCT

MA01.06 LONG-TERM FOLLOW-UP OF SMALL PULMONARY GROUND-GLASS NODULES STABLE FOR 3 YEARS: PROPER FOLLOW-UP PERIOD AND RISK FACTORS FOR SUBSEQUENT GROWTH

Jaeyoung Cho, Eun Sun Kim, Se Jong Kim, Yeon Joo Lee, Jong Sun Park, Young-Jae Cho, Ho Il Yoon, Jae Ho Lee, Choon-Taek Lee
Internal Medicine, Seoul National University Bundang Hospital, Seongnam/Korea, Republic of Korea

Background: It is uncertain how long persistent and stable ground-glass nodules (GGNs) should be followed although a minimum of 3 years is suggested. Here, we aimed to evaluate the proportion of GGNs showing subsequent growth after initial 3 years among GGNs that had been stable during the initial 3 years, and to determine clinical and radiologic factors associated with subsequent growth.

Methods: We retrospectively analyzed patients who underwent lung computed tomography for the initial 3-year follow-up period in a stable GGN that had been followed for initial 3 years. We performed a by-nodule comparison between nodule classification by the triage algorithm and the corresponding GT in the first round. At each step of the triage algorithm, we evaluated Sensitivity (Se), Specificity (Sp), Positive Predictive Value (PPV) and Negative Predictive Value (NPV).

Results: Sensitivity of the triage algorithm for classifying nodules into size categories was for 96.6% for NODCAT2, 86.9% for NODCAT3 and 90.7% for NODCAT4. Classification of GROWCAT C yielded Se=66.2% Sp=21.2%. We found an overall performance of the NELSON triage algorithm of Se/Sp 94.0%/80.3%. PPV was 11.3%, and NPV was 99.8%

Conclusion: Mathematical modeling gives valuable insights into the performance of different components of triage algorithms in lung cancer screening. We found a markedly different test performance for size verification assessment of the NELSON triage algorithm. Future work will extend the model to non-solid nodules and multiple rounds of screening. Moreover, it may have the potential to optimize triage algorithms in the design of screening programs.

Keywords: Lung Screening, Modelling, triage algorithm, volume of nodules

MA01.07 PREDICTIVE PERFORMANCES OF NELSON SCREENING PROGRAM BASED ON CLINICAL, METROLOGICAL AND POPULATION STATISTICS

Hubert Beaumant1, Nathalie Faye1, Antoine Iannissi1, Dag Wormanns4
1Sciences, Medium Technologies, Valbonne/France, 2Medical, Medium Technologies, Valbonne/France, 3Radiology, Centre Antoine Lacassagne, Nice/France, 4Radiology, Evangelische Lungenklinik Berlin, Berlin/Germany

Background: The balance of benefits and harms of screening programs depends on multiple factors such as the scenario of patient selection, the triage algorithm and the imaging methods. Because of the multifactorial nature of the outcome of screening programs, it is important to evaluate the performance of its components. We modeled the triage algorithm of the NELSON program for lung cancer screening in different scenarios in order to assess the robustness of the chosen approach. We are looking to develop a model that allows for testing the imaging protocol performance using various high-risk screening populations. Our Objective is to work out a simulator adaptive to multiple screening scenarios. In a first step, we tested a simulation of the NELSON triage algorithm by using published statistics as input data: the distribution of nodule size, the precision of nodule volume measurements and the distribution of nodules growth. Methods: We modeled the baseline round of NELSON triage algorithm. We simulated 10,000,000 ground truth (GT) data where the axial diameter of nodules followed a chi2 (df=1) distribution between 3 mm and 20 mm. For each of the GT nodule, we modeled volume measurement of the nodules by adding a Gaussian random error as documented by the Quantitative Imaging Biomarker Alliance (QIBA) screening profile. We performed a by-nodule comparison between nodule classification by the triage algorithm and the corresponding GT in the first round. At each step of the triage algorithm, we evaluated Sensitivity (Se), Specificity (Sp), Positive Predictive Value (PPV) and Negative Predictive Value (NPV).

Results: Sensitivity of the triage algorithm for classifying nodules into size categories was for 96.6% for NODCAT2, 86.9% for NODCAT3 and 90.7% for NODCAT4. Classification of GROWCAT C yielded Se=66.2% Sp=21.2%. We found an overall performance of the NELSON triage algorithm of Se/Sp 94.0%/80.3%. PPV was 11.3%, and NPV was 99.8%

Conclusion: Mathematical modeling gives valuable insights into the performance of different components of triage algorithms in lung cancer screening. We found a markedly different test performance for size verification assessment of the NELSON triage algorithm. Future work will extend the model to non-solid nodules and multiple rounds of screening. Moreover, it may have the potential to optimize triage algorithms in the design of screening programs.

Keywords: Lung Screening, Modelling, triage algorithm, volume of nodules

MA01.08 METROLOGICAL ANALYSIS OF NELSON SCREENING TRIAGE ALGORITHM: IMPACTS ON NODULE CLASSIFICATION

Mauro Rizzon1, Antonello D'Errico2, Federico Santoro1,2, Giorgio Fantin2, Massimo Ferlito1,3, Nathalie Faye1, Antoine Iannissi1
1Granelli Institute, University of Pavia, Pavia/Italy, 2Radiology, Centre Antoine Lacassagne, Nice/ France, 3Internal Medicine, Seoul National University Bundang Hospital, Seongnam/Korea, Republic of Korea

Background: Sensitivity and specificity calculations depend on multiple factors such as the scenario of patient selection, the triage algorithm and the imaging methods. Because of the multifactorial nature of the outcome of screening programs, it is important to evaluate the performance of its components. We modeled the triage algorithm of the NELSON program for lung cancer screening in different scenarios in order to assess the robustness of the chosen approach. We are looking to develop a model that allows for testing the imaging protocol performance using various high-risk screening populations. Our Objective is to work out a simulator adaptive to multiple screening scenarios. In a first step, we tested a simulation of the NELSON triage algorithm by using published statistics as input data: the distribution of nodule size, the precision of nodule volume measurements and the distribution of nodules growth. Methods: We modeled the baseline round of NELSON triage algorithm. We simulated 10,000,000 ground truth (GT) data where the axial diameter of nodules followed a chi2 (df=1) distribution between 3 mm and 20 mm. For each of the GT nodule, we modeled volume measurement of the nodules by adding a Gaussian random error as documented by the Quantitative Imaging Biomarker Alliance (QIBA) screening profile. We performed a by-nodule comparison between nodule classification by the triage algorithm and the corresponding GT in the first round. At each step of the triage algorithm, we evaluated Sensitivity (Se), Specificity (Sp), Positive Predictive Value (PPV) and Negative Predictive Value (NPV).

Results: Sensitivity of the triage algorithm for classifying nodules into size categories was for 96.6% for NODCAT2, 86.9% for NODCAT3 and 90.7% for NODCAT4. Classification of GROWCAT C yielded Se=66.2% Sp=21.2%. We found an overall performance of the NELSON triage algorithm of Se/Sp 94.0%/80.3%. PPV was 11.3%, and NPV was 99.8%

Conclusion: Mathematical modeling gives valuable insights into the performance of different components of triage algorithms in lung cancer screening. We found a markedly different test performance for size verification assessment of the NELSON triage algorithm. Future work will extend the model to non-solid nodules and multiple rounds of screening. Moreover, it may have the potential to optimize triage algorithms in the design of screening programs.

Keywords: Lung Screening, Modelling, triage algorithm, volume of nodules
MA01.07 INFLUENCE OF NODULE MORPHOLOGY ON INTER-READER VARIABILITY OF VOLUME AND DIAMETER MEASUREMENTS IN CT LUNG CANCER SCREENING

Mariolein Heuvelmans1, Daiwei Han1, Rozemarijn Vliegenthart1, Gonda De Jonge2, Joan Walter1, Peter Van Ooijen1, Harry De Koning3, Matthijs Oudkerk4

1Department of Radiology, University Medical Center Groningen, Umcg, Center for Medical Imaging- North-East Netherlands, Groningen/Netherlands, 2Department of Radiology, University of Groningen, University Medical Center Groningen, Groningen/Netherlands, 3Public Health, Erasmus MC, Rotterdam/Netherlands, 4University Medical Center Groningen, Umcg, Center for Medical Imaging- North-East Netherlands, Groningen/Netherlands

Background: The high number of false positive screen results is a major disadvantage of lung cancer screening by low-dose chest computed tomography (CT). Measurement strategy influences the false-positive rate, and nodule morphology may influence measurement of nodule size. Comparison between inter-reader variation for semi-automated volume measurements and manual diameter measurements are scarce. Therefore, we aimed to evaluate the influence of nodule morphology on inter-reader variability and assessment of growth for semi-automated volume measurements, and in manual diameter measurements. Inter-reader variability was compared to volume change cutoff at 3-month follow-up based on NELSON for nodule growth and Lung-RADS diameter cutoff. Results: For manual diameter measurements, a significant systematic deviation was found between readers in smooth, lobulated, and spiculated nodules. The deviation was up to 1.5 mm based on maximum diameter measurements. For semi-automated volume measurements, no statistically significant systematic deviation was found. Conclusion: Nodule morphology has a greater effect on size assessment based on manual diameter measurements than based on volume measurements. The larger inter-reader variability for manual diameter measurement may cause misclassification of spiculated nodules when assessing growth in 2D diameters. Therefore, an intermediate-size volume measurement is recommended for nodule size and growth determination in CT lung cancer screening.

Keywords: lung nodule, inter-reader variability, semi-automated volume measurement, manual diameter measurement

MA01.09 MORTALITY, SURVIVAL AND INCIDENCE RATES IN THE ITALIAN RANDOMISED LUNG CANCER SCREENING TRIAL (ITAL)

Eugenio Paci1, Donella Puliti2, Andrea Lopes Pegna3, Laura Carrozzi1, Giulia Picozzi1, Fabio Falaschi1, Francesco Pistelli1, Ferruccio Aquilini1, Marco Zappa1, Francesca Carozzi1, Marco Mascalchi2

1Formerly at Clinical Descriptive Epidemiology Unit, Institute for Cancer Prevention and Research (Ipsa), Florence/Italy, 2Clinical Descriptive Epidemiology Unit, Institute for Cancer Prevention and Research (Ipsa), Florence/Italy, 3Formerly at Cardio-Thoracic-Vascular Dept., Careggi Hospital, Florence; Cardio-Thoracic and Vascular Dept, University Hospital of Pisa, Pisa/Italy, 4Diagnostic Imaging Unit, Institute for Cancer Prevention and Research (Ipsa), Florence/Italy, 5Diagnostic Radiology, University Hospital of Pisa, Pisa/Italy, 6Clinical Descriptive Epidemiology Unit, Institute for Cancer Prevention and Research (Ipsa), Florence/Italy, 7Prevention Laboratory Unit, Institute for Cancer Prevention and Research (Ipsa), Florence/Italy, 8Maria Sera Department of Experimental and Clinical Biomedical Sciences, University of Florence, Florence/Italy

Background: Low Dose Computed Tomography (LDCT) screening for lung cancer (LC) is still not recommended in Europe. Methods: 71,232 invitation letters were sent to subjects registered with local General Practitioners, aged 55-69 years. From eligible respondents, we randomised 3206 eligible subjects, smokers and ex-smokers (<10 years), to the active arm receiving 4 annual LDCT (n=1631) and to control arm receiving usual care (n=1593). Each LDCT was read by 2 radiologists and the LCC was calculated and manually. Study design and performance data were already published.

Results: All subjects, enrolled from 2004-2009, were followed up for lung cancer incidence and mortality (average: 8.3 and 9.3 years, respectively). Characteristics of enrolled subjects are presented in Table1.

<table>
<thead>
<tr>
<th>Active Group</th>
<th>Control Group</th>
</tr>
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<tbody>
<tr>
<td>1613</td>
<td>1593</td>
</tr>
<tr>
<td>3206</td>
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Table1. Description of the study participants, by study arm (n=3206)

Center | Firenze | Pisa | Pistola |
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<tr>
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<tbody>
<tr>
<td>Center</td>
<td>Firenze</td>
<td>Pisa</td>
<td>Pistola</td>
</tr>
<tr>
<td>Mean age at entry</td>
<td>60.9</td>
<td>60.7</td>
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<tr>
<td>Age at entry</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;55</td>
<td>53 (3.3%)</td>
<td>64 (4.0%)</td>
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</tr>
<tr>
<td>55-59</td>
<td>687 (42.6%)</td>
<td>616 (38.7%)</td>
<td></td>
</tr>
<tr>
<td>60-64</td>
<td>497 (30.9%)</td>
<td>526 (33.0%)</td>
<td></td>
</tr>
<tr>
<td>65-69</td>
<td>371 (23.0%)</td>
<td>382 (24.0%)</td>
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<tr>
<td>&gt;69</td>
<td>5 (0.3%)</td>
<td>5 (0.3%)</td>
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Sex | Male | Female |
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<thead>
<tr>
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<tbody>
<tr>
<td>1035 (64.2%)</td>
<td>1055 (65.2%)</td>
<td></td>
</tr>
<tr>
<td>578 (35.8%)</td>
<td>544 (34.8%)</td>
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</tbody>
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Smoking status | Current | Former |
<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>1090 (65.7%)</td>
<td>575 (34.3%)</td>
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</tbody>
</table>

Keywords: lung cancer, Screening, Overdiagnosis

MA01.10 PERFORMANCE OF ACR LUNG-RADS IN THE 1ST BRAZILIAN LUNG CANCER SCREENING TRIAL (BRELT1)

Bia Rosales Santos1, Juliana Fonseca1, Mário Ghefter1, Rodrigo Chatte1, André Luiz Trajano1, Roberto Saad Junior2

1Hospital Israelita Albert Einstein, São Paulo/Brazil, 2Faculdade de Ciências Médicas Da Santa Casa de São Paulo, São Paulo/Brazil

Background: In BRELT1 we found a significant number of low dose CT (LDCT) considered positive (nodules >4 mm). The aim of this study was to assess the effect of applying ACR Lung-RADS and Pre-Test Probability of Malignancy (PTPM) in suspicious nodules >8 mm founded in a clinical CT lung screening program. Methods: Clinical LDCT (baseline and follow up) containing nodules >8 mm were retroactively reclassified using the new ACR Lung-RADSTM structured reporting system and PTPM. The model used in this study to predict the probability of malignancy was designed by Swensen et al and included patient’s age, current or former smoker, diameter of the nodule, speculation and location. All LDCT had initially been interpreted by radiologists accredited in CT lung screening reporting following the National Comprehensive Cancer Network’s Clinical Practice Guidelines in Oncology: Lung Cancer Screening (version 1.2012), which considered as positive the same criteria from the National Lung Screening Trial. Results: In BRELT1
were recruited 790 current or former smokers, with a heavy smoking history. A total of 552 nodules were found in 312 positive LDCT at baseline (39%). LDCT follow up was performed in 89.1% of this population. From them 74 patients presented solid or semi-solid nodules ≥8mm in the highest diameter. According to ACR Lung-RADS™ 39 baseline LDCT were classified as 4A (52.7%), 6 as 4B (8%), 17 as 4X (22.3%) and 10 as 2 (13.5%). Follow-up LDCT showed reduction in the category in more than 80% of cases. Using the PTPM, 44 cases were considered at moderate risk (between 6 and 60%) and 30 cases of high risk for malignancy (over 60%). None was considered low risk (5% or less). Among 26 patients who underwent biopsy in BRELIT, we found 12 cases of lung cancer, of which 90% were stage IA or IB. Conclusion: The application of ACR Lung-RADS and PTPM associated with careful multidisciplinary assessment can help in the decision process. The follow-up of patients with positive nodules requires careful analysis of the main factors related to malignancy.

Keywords: Screening, lung cancer, nodules

MA01.11 IMPLEMENTATION OF LDCT LUNG CANCER SCREENING INTO PRACTICE. RESULTS OF REGIONAL EARLY DETECTION PROGRAM

Maciej Bryl1, Beata Nikisich1, Wojciech Dyzkiewicz2, Cezary Piwkowski3, Mariusz Kasprzyk1, Wojciech Kasprzyk3, Aleksander Banin-Wojebowdski2

1Oddzial Onkologii, Wielkopolskie Centrum Pulmonologii i Torakochirurgii, Poznan/Poland, 2Oddzial Radiologii, Wielkopolskie Centrum Pulmonologii i Torakochirurgii, Poznan/Poland, 3Oddzial Torakochirurgii, Wielkopolskie Centrum Pulmonologii i Torakochirurgii, Poznan/Poland, 4Oddzial Pulmonologiczno-Internistyczny, Wielkopolskie Centrum Pulmonologii i Torakochirurgii, Poznan/Poland, 5Oddzial Pulmonologiczno-Rehabilitacyjny, Wielkopolskie Centrum Pulmonologii i Torakochirurgii, Poznan/Poland

Background: Lung cancer is the leading cause of cancer deaths both in men and women in either Wielkopolska and the whole Poland. Wielkopolska is one of Polish regions (voivodships) with about 3,4 mln inhabitants and 47% of entire population. More than 3000 patient received recommendation for further actions. Results presented are based on annual reports for regional authorities. Patients received also recommendation for further diagnostic evaluation. Finally 108 patients underwent surgery (37 lobectomies, 41 wedge resections, 30 thoracotomies/thorascopies). There were 92 cases of lung cancer confirmed (17 SCLC, 78 NSCLC, 3 carcinoid) and case of mesothelioma. Conclusion: Lung cancer screening program identifies magnitude of lung changes. Many patients require further diagnostic procedures. Most of them are fibrotic, post inflammatory changes. It is possible to diagnose lung cancer in early presymptomatic stage but numbers are low and risk models or biomarkers should be implemented to better define patients/nodules at risk.

Keywords: Screening, LDCT

SESSION MA02: RNA IN LUNG CANCER
MONDAY, DECEMBER 5, 2016 - 14:15-15:45

MA02.01 EXTRACELLULAR VESICLE MiRNAS REGULATE GENE EXPRESSION IN LOCAL LUNG ADENOCARCINOMA ENDOTHELIAL CELLS

James Lawson1, Christopher Dickman1, Rebecca Towle1, James Jabablee1, Stephen Lam1, Cathy Datnis2

1Integrative Oncology, BC Cancer Research Center, Vancouver/BC/Canada, 2Integrative Oncology, BC Cancer Agency, Vancouver/Canada

Background: Extracellular vesicles are small vesicles released from all cell types which can be used as a form of cell to cell communication. Recently these extracellular vesicles have been shown to play a key role in cancer development, growth, progression and angiogenesis. These extracellular vesicles are loaded with functional miRNAs, miRNAs and proteins which can be transferred from one cell to another. Extracellular vesicles have been known to enter neighboring cells including the surrounding stroma, and even enter biofluids. Our research shows that miRNAs transferred from lung adenocarcinoma cells through extracellular vesicles influence gene expression in endothelial cells and enhance their ability to form new blood vessels. Methods: Using 5 lung adenocarcinoma cell lines (H3295, H1437, H2073, H2228 and H23M7) we isolated extracellular vesicles using differential ultracentrifugation. RNA was extracted from the extracellular vesicles as well as the cells from which they were derived and profiled for 742 miRNAs using the miRCURY LNA Universal RT miRNA PCR system (Exiqon) to identify miRNAs that were enriched by at least 6-fold in the extracellular vesicles. Tube formation assays were conducted on a commonly used endothelial cell line HMEC-1. Results: We found an enrichment of a select set of miRNAs within lung adenocarcinoma extracellular vesicles. These miRNAs have previously been identified as tumor suppressors: miR-142-3p, miR-143-3p, miR-144-3p, miR-165-5p, miR-170-5p, miR-223-3p, miR-4283a, miR-486-5p, miR-605-5p in various cancer types. When extracellular vesicles are isolated from miR-143 and miR-165 over expressing adenocarcinoma lines they contain an increase in their over expressed miRNAs. When these miRNA enriched exosomes were incubated with HMEC-1 cells, we observed an increase in their ability to form new blood vessels and a decrease in the expression of CAMKID in the endothelial cells. miR-143-3p and miR-165-5p were also found to be enriched in serum samples draining directly from lung adenocarcinoma tumors compared to arterial serum. Conclusion: Extracellular vesicles originating from lung adenocarcinoma cells can enter endothelial cells and increase their ability to form new blood vessels through extracellular vesicle transfer of miR-143/ miR-143 suggesting that this form of communication increases angiogenesis within lung adenocarcinoma tumors.

Keywords: Extracellular Vesicle, Endothelial, microRNA, lung adenocarcinoma

MA02.02 A NOVEL 5-MIR SIGNATURE SHOWS PROMISE AS A DIAGNOSTIC TOOL AND AS A PREDICTOR OF CISPATIN RESPONSE IN NSCLC

Lauren Mac Donagh1, Steven G. Hejna2, Elaine Cuffe3, Stephen Finn1, Niamh Fitzgerald1, Vincent Young4, Ronan Ryan1, Siobhan Nicholson5, Niamh Leonard5, Kenneth O’Brien6, Martin Barry1

1Thoracic Oncology Research Group, Trinity College Dublin/st. James’ Hospital, Dublin/Ireland, 2Oncology, Hope Directorate, Dublin/Ireland, 3Dept. of Histopathology and Morbid Anatomy, Trinity College Dublin, Dublin/Ireland, 4Centre-Thoracic Surgery, Gasco Directorate, Dublin/Ireland, 5Histopathology, St. James’ Hospital, Dublin/Ireland, 6Histopathology, Labmed Directorate, Dublin/Ireland, 7Institute of Health and Biomedical Innovation, Queensland University of Technology, Brisbane/Australia, 8Thoracic Oncology Research Group, St. James’ Hospital & Trinity College Dublin, Dublin/Ireland

Background: MicroRNAs are a class of small non-coding RNAs that range in size from 19-25 nucleotides. They have been shown to regulate a number of processes within tumour biology, including metastasis, invasion and angiogenesis. More recently, miRNAs have been linked to chemoresistance in solid tumours, including lung cancer. Methods: MicroRNA expression within an isogenic panel of age-matched parent (PT) and cisplatin resistant (CisR) NSCLC cell lines was performed using the 7 th generation miRCURY LNA arrays (Exiqon). Significantly altered miRNAs within the CisR sublines were manipulated using antagonists (Exiqon) and Pre-miRs (Ambion) and functional studies were carried out in the presence and absence of cisplatin. To examine the translational relevance of these data, an isogenic model of cisplatin resistance 1x103 cells H1650 PT or CisR cells were injected into 5-7 week old NOD/SCID mice. Tumour volume was measured over time and harvested once the tumour mass measured 500mm3 and formalin-fixed, paraffin embedded (FFPE). Expression of the 5-mir signature was analysed within FFPE murine tumours and cisplatin resistance was investigated relative to cisplatin sensitive controls. Results: Profiling and subsequent validation revealed a 5-mir signature associated with our model of cisplatin resistance (miR 30a-3p, miR 30b-5p, miR 30c-5p, miR 30e-5p, miR 30f-5p). Inhibition of the miR-30 family and miR-34a-5p reduced clonogenic survival of CisR cells when treated with cisplatin. Expression of the miRNA signature was significantly altered in both adenocarcinoma (AD) and squamous cell carcinoma (SCC) relative to matched normal lung tissue and between SCC and AD tissue. miR-4283 was down regulated in SCC compared to normal control and AD sera. Similarly to the cell line expression of the miRNAs, the miR-30 family members and miR-34a-5p were up-regulated in the CisR xenograft FFPE tissue relative to PT. Conclusion: A novel miRNA signature associated with cisplatin resistance was identified in vitro, genetic
MANIPULATION OF WHICH ALTERED CLONOCIC RESPONSE TO CIPXASPIN. THE S-miR signature shows both diagnostic and prognostic biomarker potential across a number of diagnostically relevant biological mediums.

**Keywords:** MicroRNAs, Cisplatin resistance, Biomarkers

MA02. RNA IN LUNG CANCER
**MONDAY, DECEMBER 5, 2016 - 14:15-15:45**

MA02.03 EXPRESSION OF ONCOFETAL MiRNAs INACTIVATES NFB, A DEVELOPMENTAL TRANSCRIPTRION FACTOR LINKED TO TUMOUR AGGRESSIVENESS IN LUNG ADENOCARCINOMA
Dana Becker-Santos 1, Brenda Minatel 2, Kim Lonergan 1, Kelsie Thru 1, John English 1, Victoria Maclean, Calum Macaulay 1, William Lockwood 1, Wendy Robinson 1, Igor Jurisica 1, Stephen Lam 1, Wan Lam 1

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**Background:** Fetal and tumour development share striking similarities, such as intense cell proliferation, angiogenesis, increased cell motility, and immune evasion. Molecular regulators, including microRNAs (miRNAs), play important roles in both fetal lung development and in the malignant transformation of adult lung cells. Consequently, investigation of lung tumour biology in the context of lung development may reveal key regulatory mechanisms that tumours hijack from normal development, which potentially play critical roles in the pathology of lung cancer. **Methods:** 131 pairs of non-small-cell lung cancer (NSCLC) tumour and non-malignant lung tissues and 15 human fetal lung tissue samples were profiled by miRNA-sequence. Genes controlled by the oncofetal miRNAs identified were first investigated by miRNA-Data-Integration-Portal (miR-DIP) prediction, followed by luciferase-reporter assays. Associations between patient survival and mRNA expression of oncofetal miRNA-targets were evaluated in independent sample (3000 cases) using the nCounter System® (NanoString Technologies) directly on RNA, enriched of small RNA, and sixteen miRNAs. The expression analysis was performed by the nCounter System™ (NanoString Technologies) directly on RNA, enriched of small RNA, purified from the formalin-fixed and paraffin-embedded tumour tissues of 80 ADC patients. Of these 25 were predominatly lepidic (31.25%), 24 were predominatly solid (30%), 20 were predominatly acinar (16%), 11 were predominatly papillary (13.75%). **Results:** Comparing the expression results of miRNAs with the different histological ADC subtypes we found a significant higher expression of VEGF-A in papillary than in other subtypes (p<0.02). In contrast PDGFRa and PDGFRb were upregulated in lepidic and downregulated in papillary subtypes (both p<0.03). Among 16 miRNAs that target the angiogenic miR 6 were significantly downregulated in papillary compared to other groups. **Conclusion:** Our data suggest a distinct angiogenic miRNA-mRNA expression profile among the subtypes of ADC. The higher level of VEGF-A in papillary than in lepatic subtypes could represent a useful biomarker to stratify patients who can effectively treated by bevacizumb, which is directed against VEGF. Moreover, the regulation of angiogenic miRNA factors by miRNAs could provide a novel therapeutic approach based on their expression pattern specific for distinct ADC subtypes. Further studies are needed in a larger cohort of patients to confirm our results and to investigate whether different rates of response to treatment are observed among patients stratified according to the proposed biomarkers.

**Keywords:** lung adenocarcinoma subtypes, angiogenesis, VEGF-A, MicroRNAs

MA02. RNA IN LUNG CANCER
**MONDAY, DECEMBER 5, 2016 - 14:15-15:45**

MA02.07 EVALUATION OF EXOSOMAL MiRNAs FROM PLASMAs PAs TENTIAL BIOMARKER FOR NSCLC
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**Background:** Non-small-cell lung cancer (NSCLC) is one of the most common and high mortality rate carcinoma in China which biomarkers for diagnosis are limited. Therefore, novel biomarkers and methods with increased specificity for diagnosis are explored. In the present study, we revealed that nearly half of exosome miRNAs were overexpressed in NSCLC patients and 24 healthy volunteers matched with age, gender and blood collection time. Plasma exosomes were collected by 110,000g ultracentrifugation and visualized by NS3000 equipment. The raw data of exosomal miRNA profiles of NSCLC patients and healthy individuals were generated by NGS around 400× reads depth and its expression was measured by Bioinformatics tools. **Results:** In the present study, we demonstrated that nearly half of exosomal RNA was miRNA and NSCLC patients expressed a set of exosomal miRNAs with specificity compared with healthy volunteers. The expression of NSCLC patients was higher than that of healthy individuals. Furthermore, we found miR-99a-3p was significantly upregulated in NSCLC compared to normal individuals. The expression of miR-126-3p and miR-39-3p was significantly downregulated in NSCLC patients compared to healthy. However, the expression of miR-15a-5p and miR-17-5p was significantly upregulated in NSCLC compared to normal individuals. Finally, we found miR-99a-3p was the most promising biomarker for NSCLC diagnosis.

**Keywords:** NSCLC diagnosis, Exosomal miRNA
MA02.08 DEREGULATION OF CIS-ACTING LONG NON-CODING RNAS IN NON-SMALL CELL LUNG CANCER

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Background: Lung cancer remains the cause of the most cancer-related deaths each year, with a 5 year survival rate of less than 17%. Targeted therapeutics have been developed against drivers of the lung adenocarcinoma (AC) subtype, but are relevant only to the proportion of patients harbouring these genetic aberrations, emphasizing the need to explore alternative mechanisms of AC development. Natural antisense transcripts (NATs) are long, non-coding RNA (IncRNA) products expressed from the opposite strand of coding mRNAs. NATs can function in cis or trans to regulate the transcriptional activity of their cognate gene partner in either a positive or negative fashion. Here we take a novel approach to identify cis-NATs deregulated in lung AC, and explore the function of these genes with regards to their protein coding partner genes.

Methods: We performed RNA-sequencing on a set of 36 lung AC and matched non-malignant lung tissues. A sign-rank test was used to identify NATs and partner genes with significantly altered expression between tumour and matched normal tissues. These findings were validated using a Cox Proportional hazard model, as well as the log-rank test between tumor and matched normal tissues. A sign-rank test was used to compare the transcriptome of lung AC and matched non-malignant lung tissues. A sign-rank test was used to compare the transcriptome of lung AC and matched non-malignant lung tissues.

Results: Analysis of Illumina Hi-seq data from TCGA revealed the majority (78%) of deregulated sense-antisense partnerships observed in AC displayed concordant regulation. However, several discordant cis-NAT pairs were identified including an antisense to OPA INTERACTING PROTEIN 5 (OIPS), a gene required for chromatin segregation, as well as an antisense to HIGH MOBILITY GROUP A1 (HMGAI) a gene involved in the metastatic progression of many cancer types. Both the antisense to OIPS (OIPS-AS1) as well as the antisense to HMGAI (HMGAI-AS1) were significantly underexpressed in AC, while we find the overlapping protein coding partner genes to be significantly overexpressed, suggesting that these genes may negatively regulate their sense counterparts. In addition both OIPS and HMGAI are significantly associated with 5-year survival. Patients with higher expression levels of either of these genes had a significantly shorter overall survival time than patients with low expression levels, highlighting the potential clinical importance of these genes.

Conclusion: This study characterizes the landscape of antisense expression in AC and highlights novel mechanisms of oncogene regulation through natural antisense transcripts. Characterizing these oncogene regulatory mechanisms could uncover therapeutic intervention points and further our understanding of AC biology.

Keywords: lung adenocarcinoma, lung non-coding RNAs, gene regulation

MA02.09 LONG NON-CODING RNA EXPRESSION FROM PSEUDOGENE LOCI AS A NOVEL MECHANISM OF CANCER GENE REGULATION

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1Integrative Oncology, BC Cancer Research Centre, Vancouver/BC/Canada; 2Integrative Oncology, BC Cancer Research Centre, Vancouver/Canada; 3Integrative Oncology, BC Cancer Agency, Vancouver/Canada; 4Department of Integrative Oncology, British Columbia Cancer Research Center, Vancouver/Canada

Background: The advent of next generation sequencing has lead to the discovery of the functional importance of non-coding RNAs (ncRNAs) in a wide variety of cellular processes, and these genes can be exploited by tumours to drive the hallmarks of cancer. Pseudogenes are DNA sequences that are defunct relatives of their functional parent genes but retain high sequence homology. Long non-coding RNAs (IncRNAs) have been shown to regulate protein-coding genes; however, complex folding patterns make IncRNA function difficult to predict. Several IncRNAs expressed from pseudogene loci have been shown to regulate the protein-coding parent genes of these pseudogenes in trans due to sequence complementarity. The biological impact of this mechanism has not been investigated in lung adenocarcinoma (LUAD). We hypothesize that expression changes in IncRNAs expressed from pseudogene loci can affect the expression of corresponding protein-coding parent genes in trans, and that these events provide an alternative mechanism of cancer gene deregulation in LUAD tumorigenesis.

Methods: We analysed RNA-seq data from 50 LUAD with matched non-malignant tissue obtained from the TCGA for both protein-coding and non-coding gene expression. Significantly differentially expressed IncRNAs located within pseudogene loci were identified by sign-rank test (p<0.001). Mann Whitney U-tests were used to identify IncRNA-pseudogene pairs which significantly correlated expression, and survival analysis was performed using a Cox proportional hazard model.

Results: Our analysis has identified 172 IncRNAs expressed from pseudogene loci that were significantly deregulated in LUAD. Remarkably, many of these IncRNAs were expressed from the loci of pseudogenes related to known cancer genes. One of these IncRNAs, CTD-2583A14.8, was expressed from a pseudogene to ubiquitin-conjugating enzyme E2 C (UBE2C), which regulates tumor growth, apoptosis, and angiogenesis through phospho-ERK1/2. We find CTD-2583A14.8 as well as the UBE2C parent gene to be significantly upregulated in LUAD tumours compared to matched normal tissue. Furthermore, tumours with higher levels of CTD-2583A14.8 have significantly higher levels of UBE2C expression than tumours with low levels of CTD-2583A14.8, indicating that CTD-2583A14.8 may positively regulate UBE2C in trans. Conclusion: Here we show expression of IncRNAs within pseudogene loci is deregulated in LUAD, and can correlate with the expression of their protein-coding counterparts. Many of these genes associated with this putative IncRNA-pseudogene-protein-coding axis have previously been implicated in cancer. Therefore, this represents an alternative mechanism of cancer gene deregulation, and may represent novel therapeutic intervention points for the treatment of LUAD.

Keywords: non-coding RNA, pseudogenes, long non-coding RNAs

SESSION MA03: EPIDEMIOLOGY, RISK FACTORS AND SCREENING

MA03.01 GENDER DISPARITIES IN NON-SMALL CELL LUNG CANCER: A SYSTEMATIC REVIEW

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Background: Although lung cancer is the second most often diagnosed malignancy in both men and women, and the biggest cancer killer of both genders, evidence suggests that the lung cancer experience differs in women compared to men. Lung cancer incidence in men has steadily decreased since the mid-1980s, while in women it has increased. Partly, these patterns reflect sex differences in smoking behavior over the previous two decades. Additional epidemiological evidence suggests that gender impacts most facets of the lung cancer experience, including the incidence, susceptibility, severity, and molecular basis of the disease. However, there is a lack of consensus on both the magnitude and etiology of these gender-based differences. The aim of this currently ongoing systematic literature review is to more precisely define this gender disparity among non-small cell lung cancer (NSCLC) patients worldwide and summarize current opinions about the molecular basis for these observations. Methods: A preliminary rapid review was launched to outline gender disparity among NSCLC patients in North America, Europe and South Asia. Independent studies were utilized from Medline; Embase; Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews for the period between 1996 and 2016. Based on these results, a systematic literature review was carried out for the period between 1996 and 2016 using Medline and Embase databases worldwide. The main outcome measures are incidence and factors influencing NSCLC between the genders. A validated scoring system was used to appraise eligible studies for methodological quality and level of evidence. Results: The preliminary rapid search identified 17 eligible articles for review. Analysis suggests that females are more susceptible to tobacco related carcinogens, have a younger age at diagnosis and higher survival rates. We also observed an increase in the inclusion of female patients in the clinical studies over this period. Based on pre-specified selection criteria, the systematic review generated a total of 367 studies which have been retrieved and considered for further analysis. We will determine gender differences in NSCLC incidence and its molecular aberration utilizing data from independent studies based on rapid analysis of observational studies published globally. Conclusion: Our systematic literature review will help validate our preliminary findings that gender disparities in lung cancer do exist. Our findings will provide a platform for policy makers, researchers and clinicians to design clinical trials and interventions that account for these disparities.

Keywords: Gender disparities, Incidence, Molecular aberration, NSCLC

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Abstracts
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MA03.02 LUNG CANCER IN WOMEN 1926 TO 2016: COLD-BLOODED ORIGINS OF AN EPIDEMIC
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Background: The epidemiologic profile of lung cancer mortality in the U.S. is highly unusual. Mortality in males began to rise rapidly early in the 1920s and continued to increase through the 1990s before leveling off. Mortality in women did not begin to rise until decades later and did not approximate mortality in men until the early years of the twenty first century. This unusual pattern of disease can be explained by review of tobacco industry documents and court records. Methods: A search was conducted in the Legacy Tobacco Documents Database at the University of California, San Francisco, as well as review of testimony and legal reports from state and federal court decisions. Results: The beginning of the epidemic of lung cancer in women in the U.S. can be reliably traced back to Easter Sunday in 1929. On that date, a publicity stunt crank event was launched by New York cigarette producer “pate of torches” supposedly representing an expression of freedom by American women who would henceforward not be constrained from smoking in public. The public relations effort was supplemented by an advertising campaign orchestrated by Chicago marketing expert Albert Lasker. Female smoking rates began to rise approximately 20 years earlier than male rates. By the mid-1970s, the cardiovascular disease mortality was in sharp increase in lung cancer cases and deaths among women. A second phase of marketing of cigarettes to women and girls in the U.S. began in the 1970s as Philip Morris executive Joseph Cullman collaborated with tennis star Billie Jean King to market a new “slim” cigarette to young women via the Virginia Slims tennis tournaments. As the slogan “You’ve come a long way baby,” a further contribution to the lung cancer mortality arose out of the efforts of the Council for Tobacco Research (CTR) and the Council for Indoor Air Research (CIAR) to manufacture controversy regarding the danger of smoking as well as involuntary second hand smoking to provide cover for legislators voting against tobacco control legislation. As a direct result, many thousands of non-smoking women have had major involuntary exposure to tobacco carcinogens in the workplace causing lung cancer. Conclusion: Lung cancer cases presenting today originated in deliberate campaigns by tobacco executives, marketers and public relations experts to convince women and girls to smoke, despite their clear understanding that the products they were aggressively marketing would inevitably result in hundreds of thousands of deaths.

Keywords: cigarettes, second hand smoke, tobacco marketing, lung cancer

MA03.03 HIGH RISK FOR SECOND PRIMARY LUNG CANCER IN TAIWANESE EARLY-ONSET FEMALE BREAST CANCER PATIENTS
Pei-Ying Lin1, Ching-Yao Yang1, Ching-Heng Lin1, Tzu-Pin Lu1, James Chih-Hsin Yang1, Chong-Jen Yu1, Kinwei Chan1, Pan-Chyng Yang1
1National Taiwan University Hospital, Taipei/Taiwan, 2Taichung Veterans General Hospital, Taichung/Taiwan, 3National Taiwan University, Taipei/Taiwan

Background: Female lung and breast cancers are two distinct disease entities in East Asia. Although studies on second primary cancers following the first breast cancer event have been carried out, no in-depth survey on double primary breast and lung cancers has been done. This study analyzed the association between these two distinct cancer types. Methods: In the exploratory cohort study, the data were obtained from the Taiwan National Health Insurance Research Database, which contained information on approximately 24.7 million insured individuals. The Taiwan Population Census and National Cancer Registry Databases were used to identify patients with breast and lung cancers. The cohort included individuals with newly diagnosed primary breast cancer between 2000 and 2011. An age- and sex-matched systematic random-sampling method was used for subject selection in the reference non-breast cancer cohort. Multivariate Cox proportional hazard regression analysis was used to determine the effects of breast cancer on the risk of lung cancer, as shown by hazard ratios (HRs) with 95% CIs. Detailed medical record and pathological reviews were done on the National Taiwan University Hospital (NTUH) patient cohort to validate the national cohort study results. The incidence rate was used as an independent incidence rate in the validation cohort. Results: A total of 88,439 patients were diagnosed with female breast cancer between 2000-2011 in the national cohort. The HR for subsequent lung cancer was 1.27 (95% CI, 1.09-1.48). When stratified by age, the HR was 27.59 for those older than 60 years, 1.75 (95% CI, 1.18-2.60) in the group aged less than 60 years. A second primary breast cancer was diagnosed at age younger than 50 years and 1.43 for those diagnosed at age older than 50 years. These results supported the national cohort study findings that early-onset female breast cancer is a relative high risk for second primary lung cancer. Conclusion: Our findings suggest a relative high risk for second primary lung cancer among patients whose primary female breast cancer is diagnosed at age less than 50 years.

Keywords: Breast cancer, Early onset, Double primary, lung cancer

MA03.05 COST EFFECTIVENESS ANALYSIS OF CT VS CHEST X-RAY (CXR) VS NO SCREENING FOR LUNG CANCER (LC) IN THE PLCO AND NLST RANDOMIZED POPULATION TRIALS (RPTS)
John Paul Flores1, Alejandro Moreno-Koehler2, Matthew Finkelman3, Jaime Caro4, Gary Strauss2
1Hematology/Oncology, Tufts Medical Center, Boston/United States of America, 2Biostatistics, Tufts Medical Center, Boston/MA/United States of America, 3Biostatistics, Tufts School of Dental Medicine, Boston/MA/United States of America, 4Evidera, Waltham/MA/United States of America, 5Hematology/Oncology, Tufts Medical Center, Boston/MA/United States of America

Background: PLCO was the first RPT to demonstrate a significant LC mortality reduction, when comparing CT to CXR-screening. Consequently, CT-screening is now being incorporated into clinical practice. Nonetheless, questions about the value of CT-screening remain given costs of CT and workup of false-positives. A prior cost-effectiveness analysis of CT-screening using NLST data concluded that CT was generally cost-effective (NEJM: 371:1793, 2014). That analysis was performed under the assumption that CXR-screening only added costs without benefit. In an independent analysis of PLCO comparing CXR to no screening, we found that CXR-screening is associated with a highly significant LC survival advantage. This benefit was unrelated to conventional screening biases, including overdiagnosis. As CXR is less expensive than CT with a lower false-positive rate, its cost-effectiveness relative to CT should be assessed. Data from PLCO and NLST allows comparison of no screening, CXR, and CT. Methods: Costs of screening, diagnostic studies, and LC treatment were calculated based on original PLCO and NLST trial data obtained from NCI. These were estimated in 2015 US dollars from the Medicare perspective. Outpatient costs were calculated using the Medicare-2015B fee schedule. Inpatient costs were calculated using a national payment average by assigning a DRG based on procedures performed. Survival data was generated using the Kaplan-Meier method for each study and mean survival was calculated using available data. These estimates were used to calculate incremental cost per life-year gained. The NLST-eligible subset of PLCO was also used to facilitate comparison of no screening, CXR, and CT. Results: Analysis of PLCO data demonstrate that CXR compared to no screening was associated with a gain of 0.0152 life-years per person at an additional cost of $244 per person for a cost-per-life-year-gained of $1,580. In the NLST-eligible subset of PLCO, CXR cost an additional $350 with a gain of 0.0262 life-years per person for a cost-per-life-year-gained of $13,377. In NLST, CT compared to CXR cost an additional $1,181 per person and with a gain of 0.0157 life-years per-person, or $75,180 per-life-year-gained. Using the NLST-eligible subset of PLCO for comparison, the ratio for CT compared to no screening was $356. Summary Conclusion: CT-screening is both effective and cost-effective and represents the optimal method of screening for LC. However, the survival advantage associated with CT-screening in comparison to no screening and relatively low cost make CXR a reasonable alternative to CT-screening, particularly in regions of the world where cost and availability limit access to CT-screening.

Keywords: CT, Screening, Cost-effectiveness, chest X-ray

MA03.06 COST EFFECTIVENESS OF CHEST SCAN SCREENING FOR LUNG CANCER IN ABESTOS OCCUPATIONAL EXPOSURE SUBJECTS: A MODEL BASED STUDY
Juliette Vella-Boucoud1, Jean Claude Paire2, Anne Dubrueci3, Patrick Brochard1, Soizic Chamignon5, Amandine Luc1, Bruno Detournay1, Christophe Paris1, Pascal Andujar2, Christos Chouaid2
1Chest Department, Hôpital Cardiologique Creteil, Creteil,France, 2Inserm U955, Issy, Creteil/ France, 3Inserm U754, Becquemont, France, 4Inserm U754, Nancy, France

Background: The National Lung Screening trial (NLST) showed that screening with low-dose computed tomography (CT) compared with chest radiography reduced lung cancer mortality. There is very few data’s on subjects with
MA03.08 QUANTIFYING SURVIVAL IN EARLY-STAGE NSCLC: IMPLICATIONS OF RELATIVE SURVIVAL VS CAUSE-SPECIFIC SURVIVAL
Kay See Tan1, Takashi Eguchi2, Prasad Adusumilli1
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Background: Cancer-related mortality can be measured by two disparate methods: relative survival (RSR), observed survival of cancer patients versus expected survival of a matched population, and cause-specific survival (CSS, based on lung-cancer-specific mortality among cancer patients). Both are vulnerable to biases. RSR depends on a comparable reference population, while CSS relies on the cause of death. Regardless, RSR is more common in population-based studies as the cause of death is uninvolved. We apply both methods to the same dataset to assess their implications among early-stage NSCLC.

Methods: Analyses included 15792 age <60 and 70/89 age ≥60 patients, with stage I (81%) or II NSCLC. Death with unknown cause was 5% of all deaths; 5-year CID for lung-cancer, other-known and other-unknown deaths were 43%, 14% and 2%. Lung-cancer 5-year CID increased with age, from 22% (≤60) to 63% (70/89); 5-year CID among stage I, II and IV was 42%, 65% and 68% among stage II. CSS were greater than RSR in all cases. Although the bias was negligible for 1-year follow-up, the deviation increases with increasing age and years of follow-up. The estimated CSS-2s were always between RSR and CSS, suggesting that RSR underestimates the true lung-cancer survival.

Conclusion: In practice, RSR is appropriate for short follow-up and aggregate summaries, while caution is advised when reporting RSR by age groups for longer follow-up. Accurate assessment of the causes of death may alleviate such biases.

Table 1. Cohort-based cumulative relative survival rates at 1, 5 and 10 years since diagnosis; lung-cancer specific survival including only death due to lung-cancer, and cause-specific survival assuming the software casematch: unknown deaths are due to lung-cancer.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Relative survival</th>
<th>Cause-specific survival</th>
<th>Cause-specific survival with unknown deaths assumed to be due to lung cancer</th>
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<tr>
<td>IA</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
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<tr>
<td>IB</td>
<td>0.90</td>
<td>0.90</td>
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<tr>
<td>IIA</td>
<td>0.85</td>
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<tr>
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<td>IVA</td>
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<td>IV</td>
<td>0.35</td>
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Additional analysis based on several assumptions of screening program efficacy. Results: Compared with no screening, with screening with low-dose CT, over a period of 2 years, will cost, for 1000 subjects of APEXS cohort 312 645 €, will provide 9.4 additional life-years. The corresponding ICER was 33 102 € per life-gained. Sensitivity analysis showed that this result is sensitive to screening program efficacy (number, stage, and survival diagnosed by the program). Conclusion: ICR of low-dose CT lung cancer program in a cohort of abestos post occupational exposure population appears as acceptable from the French health system.

Keywords: lung cancer, screening, cost effectiveness, abestos
were proportionally more common in patients with high compared to low education, both in all patients (61.9% vs 53.9%) and among non-smokers (50.7% vs 46.7%). Waiting times There were no differences in waiting times between dates of referral and diagnosis, or between dates of diagnosis and start of treatment. Multidisciplinary conference and treatment intensity The odds for treatment decisions being made in a multidisciplinary setting was higher for patients with high compared to low education (OR 1.26, 95% CI 1.04-1.51). In stage IA-IIIB disease, the likelihood to undergo surgery was non-significantly elevated in patients with high education (OR 1.26, 95% CI 0.98-1.63). Mortality In early stage disease, high education was associated with lower all-cause (HR 0.79; 95% CI 0.70-0.89) and cause-specific mortality (HR 0.76; 95% CI 0.66-0.88) after adjustment for treatment, sex, age, region, year, comorbidity, smoking, stage, histology and performance status. Conclusion: We found evidence of social gradients in diagnostic and treatment intensity in patients with NSCLC. While there were no difference in stage at diagnosis between educational groups, a lower mortality in early stage NSCLC was observed in patients with high education.

Keywords: non-small cell lung cancer, register, Sweden, socioeconomic

SESSION MA04: HER2, PS3, KRAS AND OTHER TARGETS IN ADVANCED NSCLC
Monday, December 5, 2016 - 16:00-17:30

MA04.01 NON-AMPLIFICATION MUTATION OF ERBB2 IN EGFR-MUTATED LUNG CANCER
Kyle Gowen, Balazs Halmos, Robert Hoyer, Woondong Jeong, James Suh, Julia Elvin, Jo-Anne Vergilio, Shakti Ramkissoon, Siraj Ali, Alec Schrock, James Sun, Vincent Miller, Philip Stephens, Jeffrey Boss, Laurie Gay

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Background: Amplification of ERBB2 in EGFR-mutant lung cancers is a reported mechanism of acquired resistance to tyrosine kinase inhibitor (TKI) therapy. Comprehensive genomic profiling (CGP) of NSCLC tumors shows mutation of ERBB2, most often affecting the encoded HER2 receptor at residue S310, is also prevalent, particularly in the context of EGFR L858R.

Methods: CGP was performed on hybridization-captured, adaptor ligation-based libraries for up to 315 cancer-related genes plus select introns from 28 genes frequently rearranged in cancer on 14,887 consecutive cases of lung cancer. All classes of genomic alterations (GA) were assessed simultaneously, including base substitutions, indels, rearrangements/fusions, and copy number changes. Short variants (SV) include base substitutions or indels.

Results: A total of 2,516 (16.9%) samples featured EGFR L858R amplification (amp) and SV. Of these, 2.9% (73/2,516) harbored alterations in ERBB2 (amp and/or SV). 18 samples (0.7%) harbored SV alterations in ERBB2, 14 of which were mutations at S310. ERBB2 S310 mutations were most often found with EGFR L858R. The ratio of observed to expected mutation at HER2 S310 was 3.03. The co-occurrence of HER2 S310 and EGFR L858R was highly significant (p<0.00005). The combination of EGFR and ERBB2 alterations was more common in women. The ratio of male/female with any lung cancer in this dataset was 1.1:1, whereas the ratio of male/female with any EGFR alteration was 1.7:1 and for both EGFR and ERBB2 alterations (amp or SV) was 1.3:1. Patients with a combination of EGFR and ERBB2 alterations have been shown to respond to treatment with the pan-ERBB inhibitor afatinib, or combinations of afatinib with the HER2-targeted therapy trastuzumab. Conclusion: Short variant alterations in EGFR may be an additional mechanism for tumors to acquire resistance to treatment with EGFR-targeted TKIs. Mutations at residue S310, in the extracellular domain of HER2, are the most common ERBB2 SV observed in EGFR-mutant lung cancer, and are significantly associated with EGFR L858R. The co-occurrence of alterations in ERBB2 and EGFR is far more common in women than in men. Treatment with the pan-ERBB inhibitor afatinib, alone or in combination with agents targeting HER2, has been shown to benefit patients with lung cancer harboring mutations in both EGFR and ERBB2.

Keywords: EGFR, comprehensive genomic profiling, NSCLC, ERBB2

MA04.02 NERATINIB + TEMSIROLIMUS IN HER2-MUTANT LUNG CANCER

MA04.03 PRELIMINARY RESULTS OF A PHASE II STUDY ABOUT THE EFFICACY AND SAFETY OF PYROTINIB IN PATIENTS WITH HER2 MUTATED LUNG CANCER

CANCERS: AN INTERNATIONAL, RANDOMIZED PHASE II STUDY

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Background: Combined inhibition of HER2 and mTOR is synergistic in models of HER2 (or ERBB2)-mutant lung cancers. PUMA-NER-4201 is an adaptive, multinational, randomized phase II study comparing the pan-HER inhibitor neratinib (Puma Biotechnology) to a mTOR inhibitor temsirolimus in patients with advanced HER2-mutant lung cancers. In stage I of the study, neratinib + temsirolimus met predefined criteria for expansion into stage II (Besse et al. ESMO 2014).

Methods: Patients with stage IIB/IV locally determined HER2-mutant lung cancers were randomized to receive oral neratinib 240 mg once daily a intravenous temsirolimus 8 mg once weekly (escalated to 15 mg/week after 3 weeks) cycle (or tolerated) with loperamide prophylaxis. Primary endpoint: overall response rate (RECIST v1.1). Secondary endpoints: duration of response, progression-free survival, overall survival, toxicity assessments (NCI-CTCAE, v4.0), ClinicalTrials.gov NCT01832767. Results: Of 62 randomized patients, 60 received ≥1 dose of neratinib: neratinib alone (n=17); neratinib + temsirolimus (n=43). Baseline characteristics: male/female 32%/68%; median age 66 years; never smokers 60%; adenocarcinoma 98%. HER2 (or ERBB2) mutation type: exon 20 insertions 93.5%; missense substitutions 3.2%; unspecified 3.2%. The most common HER2 allele was A775_G776insY. Exploratory biomarker analysis from available tumor and plasma samples will be presented at the meeting. Efficacy and safety results are shown in the table. With loperamide prophylaxis, the incidence of grade 3 diarrhea was 12% with neratinib and 14% with neratinib + temsirolimus, which produced responses lasting 2 to 18+ months in 19% of patients with HER2mutant lung cancers. Correlative data will be presented at the meeting. Diarrhea was manageable with loperamide prophylaxis.

Keywords: NSCLC, Neratinib, Temsirolimus, lung cancer
**MA04.05** **P53 NON-DISRUPTIVE MUTATION IS A NEGATIVE PREDICTIVE FACTOR FOR OS AND PFS IN EGFR M+ NSCLC TREATED WITH TKI

**Julia Roeper**, Maria Netchaeva, Anne Lueers, Prenzel Regina, Nicole Roarty, Ferdinandos Skoulidis, Pia F. Hoffmann, Humam Kadara, Fortunato Bianconi, John Heymach, Anne Lueers, Nicole Roarty, Ferdinandos Skoulidis, Pia F. Hoffmann, Humam Kadara, Fortunato Bianconi, John Heymach, 1 Department of Medical Oncology, Shanghai Pulmonary Hospital, Shanghai/China, 2 Department of Medical Oncology, Shanghai Pulmonary Hospital, Shanghai/China, 3 Department of Medical Oncology, Shanghai Pulmonary Hospital, Shanghai/China, 4 Department of Medical Oncology, Shanghai Pulmonary Hospital, Shanghai/China, 5 Medical Oncology, Shanghai Pulmonary Hospital, Shanghai/China

**Background:** KRAS is the most frequently mutated oncogene in Non-Small Cell Lung Cancer (NSCLC) and plays a role as prognostic and predictive biomarker. KRAS is a key player in the MAPK signaling network driving this subgroup of pulmonary malignancies. Methods: Twenty Stage IV Formalin-fixed, paraffin-embedded (FFPE) NSCLCs were collected from chemo-naïve patients at S. Maria della Misericordia Hospital (Perugia, Italy). Ten tumors were KRAS-wild-type (KRAS-WT) and ten were KRAS-Mutant (KRAS-MUT). Whole-tissue lysates were obtained for all samples. The signaling network analysis was performed using the Reverse Phase Protein Array (RPPA) platform to quantitatively evaluate the expression/activation of 148 key proteins and phosphoproteins involved in cellular growth, survival, proliferation, apoptosis, autophagy, inflammation, invasion and cell motility. Wilcoxon Rank-Sum Test was used to compare the signaling architecture of KRAS-MUT and KRAS-WT tumours. All p-values<0.05 were considered significant. Non-parametric correlation analysis was performed to explore the signaling interconnection within each group of patients. Only correlations with p<0.0001 were considered significant. Results: This preliminary analysis revealed a statistically significant different activation level of 20 proteins between the KRAS-MUT and KRAS-WT samples. Five of the proteins that were statistically different in the KRAS-MUT group were involved in the inflammatory immunoreponse (ASK1 S183 p<0.01, Axl Y702 p<0.01, Stat2 Y690 p=0.001, Tyk2 Y1054/S1055 p=0.01 and Twist p=0.001) and six in cell cycle control and DNA repair (ATM S1981 p=0.01; Bcl-xL p=0.03; Cleaved Caspase 3 D175 p=0.02; Histone H3 S10 p=0.03; p53 S15 p<0.01; p27 T17 p=0.04). The analytes that were statistically significant were all lower in the KRAS-MUT group compared to the WT (except for p27 T17 which decreased in the KRAS-MUT group compared to KRAS-WT). Pair-wise correlation analysis revealed an overall more perturbed protein-protein interaction network and pathway activation (included AKT/mTOR signaling pathway) in the KRAS-MUT population with high number of statistically significant correlations compared to the KRAS-WT group. Conclusion: This pilot study indicated that the effect of KRAS mutation status on protein signaling in NSCLC was an alteration of the immunoreponse axis and DNA repair network. If validated in a larger cohort of patients, these results could have important clinical implications for stratification KRAS-MUT advanced NSCLC patients towards more efficacious targeted treatment and to identify new therapeutic targets based on multi-targets/multi-pathways KRAS inhibitory approach. (AIRC-supported study.)

**Keywords:** RPPA, KRAS, signaling networks, advanced NSCLC

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**MA04.06** **SIGNALLING NETWORKS IN KRAS-MUTANT ADVANCED NSCLC: A COMPLEX LANDSCAPE INVOLVING IMMUNORESPONSE, INFLAMMATION AND DNA REPAIR

**Sara Baglivo**, Elisa Baldelli, Lucio Crino, Vienna Ludovini, Rita Chiarri, Giulio Metro, Chiara Beninati, Alex Hodge, Annaamaria Siggillino, Francesca Romana Tofanietti, Ting Dong, Lorena Pistola, Fortunato Bianconi, Angelo Sidoni, Vincenzo Minniti, Emiliano Petrinicci, Mariaelena Pierobon, 1 Medical Oncology, Santa Maria Della Misericordia Hospital, Perugia/Italy, 2 Center for Applied Proteomics and Molecular Medicine, George Mason University, Manassas/United States of America, 3 Department of Experimental Medicine, University of Perugia, Perugia/Italy, 4 Department of Experimental Medicine, Pathological Anatomy and Histology Unit, University of Perugia, Perugia/Italy

**Background:** KRAS is frequently mutated in cancer, and poor response to targeted TKI therapy has been observed. The aim of our study was to investigate a potential impact of KRAS mutations on treatment outcome.

**Methods:** A phase II trial was undertaken to investigate the efficacy and safety of afatinib in patients with KRAS mutant advanced NSCLC and to correlate alterations with clinical characteristics and EGFR and KRAS mutations within a cohort of patients with lung cancer treated with afatinib. PFS was statistically significant for patients with KRAS mutation (p = 0.04). The analytes that were statistically significant were all lower in the KRAS-MUT population compared to the WT (except for p27 T17 which decreased in the KRAS-MUT group compared to KRAS-WT). Pair-wise correlation analysis revealed an overall more perturbed protein-protein interaction network and pathway activation (included AKT/mTOR signaling pathway) in the KRAS-MUT population with high number of statistically significant correlations compared to the KRAS-WT group. Conclusion: This pilot study indicated that the effect of KRAS mutation status on protein signaling in NSCLC was an alteration of the immunoreponse axis and DNA repair network. If validated in a larger cohort of patients, these results could have important clinical implications for stratification KRAS-MUT advanced NSCLC patients towards more efficacious targeted treatment and to identify new therapeutic targets based on multi-targets/multi-pathways KRAS inhibitory approach. (AIRC-supported study.)

**Keywords:** RPPA, KRAS, signaling networks, advanced NSCLC

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**MA04.07** **IMPACT OF MAJOR CO-MUTATIONS ON THE IMMUNE CONTEXTURE AND RESPONSE OF KRAS-MUTANT LUNG ADENOCARCINOMA TO IMMUNOTHERAPY

**Ferdinandos Skoulidis**, Yasir Elamin, Vassiliki Papadimitrakopoulou, Tong Pang, Jing Wang, Jeff Lewis, Wasee Rensongkawong, Caleb Chu, Emily Roarty, Jianjun Zhang, Hai Tran, Jaime Rodriguez-Canales, Edwin Parra, Carmen Behrens, Humam Kadaa, Ignacia Wistuba, John Heymach, 1 Thoracic, Head & Neck Medical Oncology, The University of Texas M. D. Anderson

**Background:** KRAS is the most frequently mutated oncogene in NSCLC. Major co-mutations have important clinical implications for stratification of KRAS-MUT NSCLC patients towards more efficacious targeted treatment and to identify new therapeutic targets. Methods: We performed protein expression profiling of 77 NSCLC patients at S. Maria della Misericordia Hospital (Perugia, Italy), using the Reverse Phase Protein Array (RPPA) platform. Median survival times were longer in patients with co-mutations compared to KRAS-MUT patients. Conclusion: This study indicates that major co-mutations have an important clinical impact on the immune contexture and response of KRAS-MUT NSCLC to immunotherapy.
MA04.09 RICTOR AMPLIFICATION IN NON-SMALL CELL LUNG CANCER: AN EMERGING THERAPY TARGET

Jeffrey Ross1, Haiying Cheng2, Roman Perez-Soler1, James Suh1, Dean Pavlick1, Siraj Ali1, Alexis Schrock1, Julia Elvin1, Jo-Anne Vergilio1, Shakti Ramkisson1, David Vincent1, Martin eller2, Philip Stephens1, Laurie Gay1

1Foundation Medicine, Cambridge/MA/United States of America, 2Oncology, Montefiore Medical Center, Bronx/NY/United States of America

Background: Comprehensive genomic profiling (CGP) can discover novel therapy targets in NSCLC. Amplification of RICTOR, encoding a component of the mTORC2 complex, has recently been identified as a targetable alteration leading to clinical benefit. Methods: CGP was performed on hybridization-captured, adaptor ligation-based libraries for up to 315 cancer-related genes in more than 2,000 patients with NSCLC. Results: Mutations in RICTOR were observed in 9/17 (52.9%) of PR, 3/12 (25%) of KR, and 0/6 (0%) of KL tumors (P=0.049, Fisher’s exact test, 2x3 contingency table). In contrast, co-mutation defined KRAS subgroups exhibited significantly different median FPF to PFS (P=0.0014, log-rank test) and 0% to ROR to immune checkpoint inhibitors (P=0.88, Fisher’s exact test, 2x3 contingency table). There was no impact of different RAS alleles (G12C/G12V/G12D) on FPF (P=0.364), log-rank test. Objective responses were observed in 9/17 (52.9%) of PR and 3/12 (25%) of KL tumors compared to 0/6 (0%) of KR tumors (P=0.049, Fisher’s exact test, 2x3 contingency table). In the PROSPECT cohort of surgically resected LUACs with available whole exome sequencing data, somatic mutation in STK11 was associated with reduced intra-tumoral densities of CD3+ (P=0.0016), CD8+ (P=0.0025) and CD4+ (P=0.0036) lymphocytes. Conclusion: Mutations in STK11/LKB1 are associated with an inert tumor immune microenvironment and poor clinical response of KRAS-mutant LUAC to immune checkpoint blockade. The mechanism that underlies this phenotype and strategies to overcome it are under investigation. The impact of additional co-mutations on the immune response and response of KRAS-mutant LUAC to immunotherapy is also being explored.

Keywords: KRAS, Immunotherapy, STK11, Co-Mutations

MA04.10 LUNG CANCER GROWTH IS SUPPRESSED BY CD26/DPP4-INHIBITION VIA ENHANCED NK CELL AND MACROPHAGE RECRUITMENT

Jae-Hwi Jang1, Florian Janker1, Stephan Arni1, Yoshito Yamada1, Walter Wieder1, Wolfgang Jungraithmayr1

1Thoracic Surgery, University Hospital Zurich, Zurich/Switzerland

Background: Lung cancer is the leading cause of death among cancers. There is broad evidence that immune cells are involved in the growth and development of these malignancies. CD26/DPP4 (dipeptidyl peptidase 4) is a transmembrane glycoprotein, that is constitutively expressed on hematopoietic cells, but also found on lung epithelial and endothelial cells. We found previously that the activity of CD26/DPP4 of lung cancer patients at early stages is four times higher than in normal tissue. Here, we tested whether CD26/DPP4-inhibition is able to modulate lung cancer growth in mice.

Methods: An orthotopic lung tumor model was employed by sc. injections of the mouse lung cancer (Lewis Lung Carcinoma (LLC)) and a human adenocarcinoma cell line (H460). These were developed in mice C57BL6 (n=18) and CD1-nude mice (n=20) respectively. The CD26/DPP4-inhibitor Vildagliptin was given in drinking water of 50mg/kg daily dose. Tumor growth was evaluated by wet weight of tumor mass at 2 weeks. Histological assessments included TUNEL, immunohistochemistry (IHC) of CD3, CD200, F4/80 and Nkp46. IL-10, Arginase, IL12, NKP46, Nk1, IFN g, Granyme, and Perforin 1 were analyzed by RT-PCR. In vitro analysis of surfactant protein (SP) expression in LLC and H460 were performed by western blotting. For a proof of concept, macrophage ablation was performed by clodronate-liposome during Vildagliptin treatment.

Results: Vildagliptin treatment significantly reduced the tumor growth of both, LLC and H460 in mice. IHC showed macrophages (F4/80+) and NK cells (NKP46+) to be significantly increased by Vildagliptin with tumors, while TUNEL stain and IHC of IFN g and B-cell infiltration did not show any difference. Gene expression levels of anti-inflammatory markers (IL-10, and Arginase) were unchanged, while the pro-inflammatory cytokine IL-12 was significantly elevated. The NK cell markers Nkp46, Nk1.1, IFN g, Granyme and Perforin 1 were significantly upregulated within the tumor by Vildagliptin, indicating that inhibition of CD26/DPP4 recruits NK cells into the tumor. Furthermore, we found enhanced SP expressions in lung cancer cell lines by Vildagliptin treatment in vitro. Macrophage ablation with clodronate-liposome in Vildagliptin treated mice reversed the tumor size significantly.

Conclusion: The inhibition of CD26/DPP4 decreased lung cancer growth in primary models of mouse and human lung cancer and increased inflammatory macrophages and NK cell cytotoxicity within those tumors. Furthermore, an increased expression of SP by Vildagliptin treatment in lung cancer cell lines suggests that surfactant production in lung cancer activates macrophages to fight against lung cancer via the recruitment of macrophages and NK cells.

Keywords: Lung; Cancer; CD26/DPP4; Immunity

MA04.11 MECHANISTIC INSIGHTS INTO CAR T-CELL EFFICACY IN THE TREATMENT OF HETEROGENEOUS ANTIGEN EXPRESSING LUNG ADENOCARCINOMA

Aurore Morello1, Masha Zeltsman1, Adam Bograd1, David Jones1, Prasad Adusumilli1

1Therapeutic Oncology, Montefiore Medical Center, Bronx/NY/United States of America

Abstracts
Fluoroscopy was used in all. Sampling included bronchial washing and brushing (if no direct vision) or biopsy (if lesion directly visualized). Statistical analyses R 2.3.3. (Results: Total of 63 patients (VBN and non-VBN, 21:42). Clinical characteristics are in table 1. Diagnostic yield was 75% vs 43.9% (p=0.029). Factors associated to positive diagnosis in table 2. Further diagnostic techniques were needed in 14% vs 52% (p=0.001). No differences seen in procedure duration or complications.

| Table 1. Clinical characteristics (n=63) |
|-----------------|-----------------|-----------------|
| Age             | VBN             | Non-VBN         |
| Age (y)         | VBN             | Non-VBN         |
| Male            | VBN             | Non-VBN         |
| Major axis (mm) | VBN             | Non-VBN         |
| Average axis (mm)| VBN             | Non-VBN         |
| Solid lesion (%)| VBN             | Non-VBN         |
| TC localization | VBN             | Non-VBN         |
| Periphery       | VBN             | Non-VBN         |
| Medial          | VBN             | Non-VBN         |
| Central         | VBN             | Non-VBN         |
| Bronchial       | VBN             | Non-VBN         |
| Bronchus sign   | VBN             | Non-VBN         |
| Artery sign     | VBN             | Non-VBN         |
| PET/CT available | VBN             | Non-VBN         |
| SUV max (mGy)   | VBN             | Non-VBN         |
| Malignant lesions| VBN             | Non-VBN         |

Conclusion: ULTRATHIN BRONCHOSCOPY may increase the diagnostic yield of lung bronchoscopy for diagnosing peripheral pulmonary lesions, especially those located in the utmost periphery and fluoroscopically not visible. Therefore, use of VBN reduces the need for further diagnostic procedures. Funded by La MaratóTV3-20133510, FIS-ETES PI09/0917, FUCAP and SEPAR.

Keywords: Peripheral Pulmonary Nodule, bronchoscopy

MA05.01 VIRTUAL BRONCHOSCOPIC NAVIGATION-GUIDED ULTRATHIN BRONCHOSCOPY FOR DIAGNOSING PERIPHERAL PULMONARY LESIONS

Martia Diez-Ferrer, Arturo Morales, Noelia Cubero, Rosa Lopez-Lisbona, Nikos Koutsos, Jordi Dorca, Antoni Rosell
Respiratory Medicine, Hospital Universitari de Bellvitge, L’Hospitalitat de Llobregat/Spain

Background: Diagnosis of peripheral pulmonary lesions with ultrathin bronchoscopy (UH) has fewer complications than transbronchial needle aspiration (TBNA). However, diagnostic yield with UTH is lower. Virtual bronchoscopic navigation (VBN) might increase diagnostic performance of UTH. The main objective was to compare diagnostic yield of UTH with and without VBN. Methods: Prospective case-control study paired 1:2 for lesion size and localization, bronchus sign, sex and final diagnosis. LungPoint (Broncus, USA) was used to plan and navigate based upon online image analysis, putting endoscopic and virtual images in correspondence. Factors associated to positive diagnosis in table 2. Further diagnostic techniques were needed in 14% vs 52% (p=0.001). No differences seen in procedure duration or complications.

Conclusion: We provide a mechanistic reason for the antigen-specific, bystander efficacy of CAR T cells against low antigen-expressing lung cancer cells. Strategies to augment LFA-ICAM interactions between CAR T cells and cancer cells can effectively translate mesothelin-targeted CAR T-cell therapy against heterogeneous antigen-expressing solid tumor, lung cancer.

Keywords: lung cancer, mesothelin, Immunotherapy, CAR T-cell

SESSION MA05: INNOVATIVE TECHNIQUES IN PULMONOLOGY AND THE IMPACT ON LUNG CANCER MONDAY, DECEMBER 5, 2016 - 16:00-17:30

MA05.02 ELECTROMAGNETIC NAVIGATION BRONCHOSCOPY: A PROSPECTIVE, GLOBAL, MULTICENTER ANALYSIS OF 1000 SUBJECTS WITH LUNG LESIONS

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Background: Electromagnetic navigation bronchoscopy (ENB) may aid in accessing smaller, more peripheral lesions and hence facilitate earlier diagnosis. ENB may also provide a safer alternative to transbronchial biopsy, and allow adequate tissue capture for molecular testing, diagnosis, staging, and localization for surgery in a single anesthetic event. However, usage patterns, safety, and performance remain largely unexplored in a prospective, multicenter study. Methods: NAVIGATE is a global, prospective, multicenter study of ENB using the superDimension™ navigation system (Medtronic, Minneapolis). A pre-specified 1-month interim analysis was conducted on the...
first 1,000 primary cohort subjects enrolled at 29 centers in the United States and Europe. Enrollment and 2-year follow-up are ongoing. Results: One-month follow-up was completed in 933/1,000 subjects. Of 1,000 procedures, ENB was intended for lung biopsy in 96.4%, to place fiducial markers in 21.0%, and for dye marking in 1.7% (multiple indications in 34.9%). Lymph node biopsies were attempted in 33.4% of procedures (322/334 using linear endobronchial ultrasound (EBUS)). General anesthesia was used in 79.7% and radial EBUS in 54.3%. Among 1,129 lung lesions, fluoroscopy was used in 90.1% and rapid on-site pathology evaluation in 683/1035 (66.0%). Median lesion size was 20.0 mm (interquartile range 16.0 mm). Most lesions were in the peripheral (62.6%) or middle (30.3%) lung thirds. A bronchus sign was present in 68.4% and 6.3% were ground glass. Navigation was subjectively considered successful in 1,036 lesions (91.8%). Site-reported pathology results were read as malignant in 452 lesions (63.6%), consisting of ≥2 bronchopulmonary hemorrhage and Grade 3 respiratory failures rates were 1.0% and 0.6%, respectively. ENB-related pneumothorax was 4.9% (49/1,000) overall and 3.2% Grade ≥2 based on the Common Terminology Criteria for Adverse Events scale. The ENB-related Grade ≥2 bronchial pulmonary hemorrhage and Grade ≥4 respiratory failures rates were 1.0% and 0.6%, respectively. At the same time, minimally invasive sampling techniques such as endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) result in smaller volume specimens. It has been shown that at least 3 EBUS-TBNA passes per lesion are sufficient for cytological subtyping. However, the number of passes needed for mutational subtyping is unclear. We sought to determine the adequacy of a single EBUS-TBNA for genotyping clinically actionable mutations.

Methods: Patients undergoing EBUS-TBNA for diagnosis of lung cancer were prospectively recruited. Paired samples from the same target lesion were collected on-site during EBUS-TBNA. DNA was extracted from both samples and subjected to quantitative PCR. DNA quantity was measured by DNA Integrity Number (DIN) and quality assessed using melting curve analysis.

Results: We analyzed 1,036 DNA samples from 1,000 patients. DIN was calculated in 1,033 cases (91.8%). Complete DNA quantity and quality assessment was performed in 933 (90.1%) of the 1,033 cases. A single EBUS-TBNA yields DNA of quantity and quality sufficient for targeted molecular testing in lung cancer. Conclusion: A single EBUS-TBNA yields DNA of quantity and quality sufficient for molecular analysis, and is expected to be adequate for lung cancer genotyping.

Keywords: DNA quality, DNA quantity, Molecular genotyping, ENB, ENB-related pneumothorax, quantitative PCR

Table 1. DNA quantity and quality

<table>
<thead>
<tr>
<th>Histological subtype</th>
<th>Cases, n (%)</th>
<th>Mean DNA quantity (µg)</th>
<th>Mean DNA Integrity Number (DIN)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenocarcinoma/NSCLC-NOS</td>
<td>25 (61.0)</td>
<td>3.83</td>
<td>8.8</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>10 (24.4)</td>
<td>2.65</td>
<td>9.0</td>
</tr>
<tr>
<td>Small cell lung carcinoma</td>
<td>5 (12.2)</td>
<td>5.28</td>
<td>9.0</td>
</tr>
<tr>
<td>Carcinoid</td>
<td>1 (2.4)</td>
<td>16.24</td>
<td>9.1</td>
</tr>
<tr>
<td>Overall</td>
<td>41</td>
<td>6.03</td>
<td>8.9</td>
</tr>
</tbody>
</table>

MA05.05 GENOMIC PROFILES OF LUNG CANCER ASSOCIATED WITH IDIOPATHIC PULMONARY FIBROSIS

Ji An Hwang1, Deokhoon Kim2, Soo Hyun Bae2, Sung Min Chun2, Joon Seong Song2, Mi Young Kim2, Jin Woo Song2, Woo Sung Kim2, Jae Cheol Lee2, Sojung Park2, Hyegyung Ryu2, Chang Min Choi2, Se Jin Jang2

Asan Medical Center, Seoul/Korea, Republic of Korea

Background: Idiopathic pulmonary fibrosis (IPF) is associated with an increased risk of lung cancer (LC) independent of the effect of cigarette smoking. The prognosis of IPF-associated LC (IPF-LC) is known to be worse than the lone IPF or LC mainly due to the complications accompanying LC treatment with no established or standardized consensus. However, despite recent progress in the understanding of pathogenesis and the treatment of LC in general population based on the advances in molecular genomics, the pathogenesis or molecular profiles of IPF-LC has been largely unknown to date.

Methods: We assessed genomic profiles of IPF-LC using targeted exome-sequencing (OncoPanel version 2) in 35 matched tumor/normal pairs surgically resected between 2011 and 2014. Whole genome-sequencing calling were performed using GATK HaplotypeCaller and MuTect with GATK SomaticIndelocator, respectively. Copy number analysis was conducted using CNVkit with focal events determined by GISTIC 2.0, and pathway analysis (KEGG) using DAVID. Results: Germline mutations in TERT (rs2736100, p=33) and CDKN2A (rs2395655, p=721) were detected in 39.4% and 43.9% of IPF-LC patients, respectively. A single EBUS-TBNA yields DNA of quantity and quality sufficient for targeted molecular testing in lung cancer. Conclusion: IPF-LC is genetically characterized by the presence of somatic mutations reflecting viral and immune-related mutagenic processes in the background of specific germline mutations, and is associated with potentially targetable alterations such as BRAF mutations.

Keywords: idiopathic pulmonary fibrosis, genomics, lung cancer
having COPD, 48.4% underwent spirometry. 30.2% of individuals with lung cancer were also diagnosed with COPD and 60.8% underwent spirometry at any time. Among those with a diagnosis of both lung cancer and COPD, 73.6% underwent spirometry. For individuals with registry recorded stage data, 12,110 persons had stage I-II lung cancer, of whom 90.7% had spirometry and 55.9% had a diagnosis of COPD. Conversely, among 31,392 persons with stage III-IV lung cancer, 54.6% had spirometry and 46% were diagnosed with COPD (p < 0.001 vs early stage for both). Conclusion: The diagnosis of COPD is not based on spirometry in half of cases. More patients with early stage lung cancer underwent spirometry and a higher rate of spirometry was associated with more diagnosis of COPD. Increased use of spirometry may improve the accuracy of a COPD diagnosis and may increase the diagnosis of COPD in advanced stage lung cancer, allowing improved dyspnea management in this population.

Keywords: dyspnea, lung cancer, emphysema, spirometry

MA05.07 IDENTIFYING COMORBID DISEASE ON CHEST CT SCANS IN A LUNG CANCER SCREENING-ELIGIBLE COHORT
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Background: Lung cancer screening (LCS) with chest CT scans in high-risk smokers has been demonstrated to save lives. Medicare and private insurers now cover these scans for beneficiaries under specific criteria. However, most smokers will die of comorbid smoking-related diseases rather than lung cancer itself. Important information about comorbid conditions is available on screening chest CT scans, but the prevalence of these comorbidities has not been comprehensively assessed. Methods: COPDGene subjects from the Phase 1 visit who met USPSTF criteria for LCS (age <55, >30 pack years smoking, current or former smokers within 15 years of smoking cessation or current smokers) were assessed for coronary calcification, emphysema, gas trapping, airway wall thickening and vertebral bone density based on standard dose CT scans. A new diagnosis of emphysema, osteoporosis, or cardiovascular disease was assumed when there was no self-report of diagnosis or medication use. Results: In 76% of CT scans from LCS-eligible COPDGene subjects, we found abnormal emphysema (>5% low attenuation area @-950 Hounsfield units), airway wall thickening or gas trapping (>20% low attenuation area @ -856 Hounsfield units). Osteoporosis was identified in 54% of all CT scans, and abnormal coronary artery calcium was present in 51%. In non-COPD smokers a new diagnosis of emphysema, osteoporosis or coronary calcification was found in 74I (48%) subjects. Overall, 75% of LCS-eligible CT scans showed one or more non-cancer diagnoses. Conclusion: Enhanced readings of the lung cancer screening scans could identify individuals with previously undiagnosed osteoporosis, atherosclerotic heart disease, emphysema and COPD. Identification and treatment for these conditions may reduce morbidity and mortality, improve quality of life and enhance smoking cessation.

Keywords: Screening, emphysema, coronary artery disease, osteoporosis

MA05.09 THERE IS A CLOSELY RELATION BETWEEN EXHALED NITRIC OXIDE AND RADIATION PNEUMONITIS
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Background: Radiation pneumonitis is a major toxicity after the thoracic radiotherapy, with no method available to accurately predict the individual risk. This was a prospective study to evaluate the exhaled nitric oxide as a predictive biomarker for radiation pneumonitis in the patients received the thoracic radiotherapy Methods: A total of 68 patients with lung cancer or esophageal cancer, who received the thoracic radiotherapy, were enrolled in the present study. Each patients underwent the exhaled nitric oxide measurement before the radiotherapy and at the end of radiotherapy. Pneumonitis toxicity was scored using the Common Terminology Criter
Results: Of the 68 patients, 65 were evaluable. The pneumonitis toxicity grade were grade 3 for 6, grade 2 for 11 and grade0-1 for 48. The exhaled NO measured before radiotherapy and at the end of radiotherapy were 23.0±5.98 (range 10-53) and 22.8±6.8 (range 11-60) ppb. For the exhaled NO ratio, the AUC is 0.879 (95% CI 0.77% - 0.94%). The accuracy of predicting the symptomatic patients was identified “good” according to the predictive ability criteria and the optimal cutoff value was tested as 1.305. For the exhaled at the end of RT, the AUC is 0.77% (95% CI 0.65%-0.892). The accuracy of predict the symptomatic patients was evaluated “fair”, The optimal cutoff value was identified as 19.5 ppb. Conclusion: The exhaled nitric oxide ratio>1.305 or the exhaled nitric oxide at the end of radiotherapy>19.5 ppb was found to have a closely relation with radiation pneumonitis.

Keywords: Radiation pneumonitis, radiation oncology, exhaled Nitric Oxide

MA05.10 CELL-FREE DNA TESTING FOR EGFR MUTATIONS IN CLINICAL PRACTICE - FACTS AND FIGURES FROM AN AUSTRIAN LUNG CANCER CENTER
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Background: Detection of EGFR mutations using cell-free DNA in plasma has recently emerged as a novel diagnostic approach to lung carcinoma. This “liquid biopsy” (LB) may also be useful for monitoring disease activity in EGFR-mutated tumors as well as in the management of EGFR-tyrosine kinase inhibitor (TKI) therapy. We present data collected in one year of use and report on applicability and diagnostic value in daily clinical practice. Methods: EGFR Mutations were analyzed using the semi-quantitative Roche cobas® EGFR Mutation Test v2, comprising 42 mutations. Cell free DNA was extracted from EDTA-Blood with the Qiagen QIAsymphony circulating DNA Kit. LB was initially used for follow-up of known EGFR-mutated tumors and/or in patients under TKI-therapy. Subsequently, we introduced routine LB testing in the primary diagnostic workup of lung cancer patients. Results: From July 2015 to June 2016 we performed a total of 92 liquid biopsies in 77 patients (60% male, mean age 65y) in whom EGFR mutations could be detected in 10 cases (13%). EGFR status from histological samples was available in 40 patients, in 14 (18%) of them mutations were reported. Compared to histological EGFR status, LB reached a sensitivity and specificity of 0.57 and 0.96, respectively. A total of 9 patients had multiple LB testing during follow-up. Three of them initially had detectable mutations by LB, which turned undetectable upon tumor-specific treatment. Two patients remained EGFR-positive during follow-up despite of therapy, whereas four patients remained negative throughout follow-up and therapy. Resistance mutations under TKI-therapy were not observed. Primary LB (before initiation of any tumor-specific therapy) was obtained from 47 patients (72% male, mean age 66y). EGFR mutations by LB were detected in 2 patients (4%, 1 Ins. Exon-20, 1 L858R), while histology revealed EGFR mutations in 2 out of 22 patients (9%, both L858R). Comparison yielded a sensitivity of 0.5 and a specificity of 0.95 for LB. Conclusion: Testing for EGFR mutations using cell-free DNA has been established as a new powerful tool in the field of pulmonary oncology. Apart from sole detection of EGFR mutations, especially the application of LB in following patients over time will provide valuable new opportunities in clinical routine and decision making.

Keywords: liquid biopsy, EGFR mutation, follow-up, TKI

MA05.11 PHOTODYNAMIC THERAPY FOR PERIPHERAL LUNG CANCER USING COMPOSITE-TYPE OPTICAL FIBERSCOPE OF 1.0 MM IN DIAMETER
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Background: Photodynamic therapy (PDT), is a treatment modality for many cancers, and uses a tumor-specific photosensitizer and laser irradiation. PDT is recommended as a treatment option for centrally located early lung cancer. The detection of peripheral lung cancers is increasing, and stereotactic body radiotherapy (SBRT) and percutaneous thermal ablation are emerging as...
MA06.01 OVERALL SURVIVAL CHARACTERIZATION OF INCIDENTAL N2 NON-SMALL CELL LUNG CANCER OVER 14 YEARS AT A SINGLE CANADIAN INSTITUTION
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Background: Incidental stage IIA non-small cell lung cancer (NSCLC) cases have positive N2 mediastinal lymph node involvement discovered at the time of surgery, resulting in stage reclassification. These patients represent a small group within the stage III patient spectrum with limited data regarding their outcome. This study’s aim is to characterize the survival of incidental stage IIA disease and compare these outcomes to patients diagnosed with stage II and I IIA disease. Methods: Using the Glans-Look Lung Cancer database and electronic patient charts, a retrospective review identified patients consulted at the Tom Baker Cancer Center from 1999 to 2012 who were defined as incidental stage II NSCLC. Their outcome was compared with stage II patients who underwent resection and stage IIIA patients treated with neoadjuvant therapy, restaging, and radiation (CTRT). These groups were selected for comparison because they represent patients who received the recommended care for their respective diagnosis. A Kaplan-Meier analysis was conducted to compare overall survival (OS) among the groups. Results: Fifty-eight incidental stage II NSCLC patients were identified: median age was 63 years (SE ±10.3), 66.6% male, and 63.8% received adjuvant therapy. There were 225 individuals treated with CCR; median age 64 years (SE ±9.0), 56.0% male. The stage II group contained 248 individuals, the median age was 64 years (SE ±10.2), 53.6% were males, and 36.4% received adjuvant therapy. The OS of the incidental group was 47.4 months (95% CI 20.0-74.7). The OS for patients treated with CCR only was 24.0 months (95% CI 20.8-27.2) and 53.3 months (95% CI 43.7-66.9) for stage II resected cases. There was a significant difference in OS between CCR-treated stage IIA and incidental cases (p < 0.001) but not between stage II and incidental (p = 0.264). The five-year survival rates were 64.4% (SE ±6.5) for incidental IIA, 21.0% (SE ±12.7) for CCR-treated IIA, and 66.9% (SE ±12.2) for resected stage II. Conclusion: This study demonstrates that incidental stage IIA-IIIB NSCLC patients are a distinct group whose median OS closely resembled stage II patients. The benefit of resection for stage IIA patients suggests that the traditional influence of stage in dictating treatment is changing. Further investigation is needed to identify which stage IIA patients benefit the most. Ongoing analysis will include a comparison of progression-free survival between the three groups, impact assessment of post-operative treatment on OS, and a description of the diagnostic process evolution over time leading to an incidental II diagnosis.

Keywords: Incidental, outcomes, locally advanced disease

MA06.02 DOES PATHOLOGICAL STAGING FOLLOWING NEOADJUVANT THERAPY (YPTNM) REFLECT THE REALITY?
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Background: Complete histopathological response or downstaging has been reported as a good prognostic factor for locally advanced non-small cell lung cancer (NSCLC) patients who received neoadjuvant therapy and underwent surgical resection. However, it is yet to be known if the prognosis of ypStage I patients is similar to that of ypStage I cases. In this study we will compare the long-term survival following surgical excision between locally advanced NSCLC that have been downstaged to stage I after neoadjuvant therapy versus stage I NSCLC treated by direct surgery. Methods: In this is a multi-centered study we retrospectively analyzed the medical data of NSCLC patients undergoing surgery (segmentectomy or more) between January 1998 and December 2014. According to the histopathological results patients with stage I (T1a-N0-D0) disease (n=427) were included into the study. Patients were divided into two groups Group 1: patients who underwent direct surgical resection without any preoperative therapy (n=291), Group 2: Patients who had locally advanced stage IIA (ypStage IIA) and received neoadjuvant treatment (chemotherapy or chemoradiation) for locally advanced NSCLC (n=136). The survival rates and effecting factors were analyzed. Results: All but 64 patients were male with a mean age of 60y (20-87y). According to tumor type; 192(45%) patients had squamous cell carcinoma, 158(37%) adenocarcinoma and 175(42%) NSCLC. Neoadjuvant treatment consisted of chemotherapy in 89 (65,4%) and chemoradiation in 47(34,5%) patients. Histopathological investigation of the resected specimen revealed stage Ib (T2aN0) in 205 patients (group 1; n=140, group 2; n=1=65, p<0.05). Overall mortality rate for all patients was 30,9% (132/427) with 1,8% mortality. Five year survival rate in all patients was 71% (77 in group I and 57% in group II). The difference was statistically different between the groups, p<0.001. Conclusion: This study showed that survival of patients after surgical excision was different in ypStage I compared to pStage I. Histopathological staging does not reflect the clinical outcome. Our impression is that IASLC recommendations for staging of NSCLC should be subdivided or revised according to ypTNM staging following neoadjuvant treatment.

Keywords: neoadjuvant therapy, restaging, survival, pathological stage

MA06.03 RECURRENCE DYNAMICS AFTER TRIMODALITY THERAPY (NEOADJUVANT CHEMORADIOThERAPY AND SURGERY) IN STAGE IIIA(N2) LUNG CANCER
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Background: In IIIA(N2) Non-small cell lung cancer (NSCLC), various strategies to cure have been tried but the major cause of mortality is still the recurrence. Therefore, understanding of the dynamics of recurrence is important to improve the treatment outcome. We investigated the timing and patterns of recurrence after treatment of IIIA(N2) NSCLC with trimodality treatment (neoadjuvant chemoradiotherapy and surgery). Methods: An institutional database of consecutive patients between 1997 and 2013 (N = 574) was reviewed retrospectively. Eligible patients had pathologically proven N2 disease of NSCLC and completion of a planned trimodality treatment. First events involving the development of loco-regional recurrence, distant metastases or both were considered. The hazard rate function was used to evaluate the dynamics of recurrence. Results: The 5-year overall survival rate was 47% and the 5-year recurrence free survival rate was 29%. Among the 299 patients (52.1% of total) who experienced recurrence, 26 (8.7%) had
MA06.05 SCREENING FOR BRAIN METASTASES IN PATIENTS WITH STAGE III NSCLC, MRI OR CT? A PROSPECTIVE STUDY
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Background: In all current non-small cell lung cancer (NSCLC) guidelines it is advised to screen all stage III patients for brain metastases, preferably by magnetic resonance imaging (MRI), or otherwise a contrast-enhanced computed tomography (CE-CT). Access to MRI can be problematic and a dedicated brain CE-CT can be incorporated in the staging. Fluodeoxoglucose-positive emission tomography (FDG-PET)-CT scan. The additive value of a brain MRI after a dedicated brain CE-CT scan is unknown. Methods: In this observational prospective multicentre study all consecutive stage III NSCLC patients scheduled for treatment with curative intent from three Dutch hospitals who underwent a dedicated brain CE-CT incorporated in the staging FDG-PET and an additional brain MRI were included. Patients with another primary tumour within 2 years of NSCLC diagnosis were excluded. Data regarding patient characteristics and imaging results were collected. Primary endpoint was the percentage of patients diagnosed with brain metastases on MRI without suspect lesions on CE-CT. 118 patients were needed to show a clinically relevant considered difference of 2%. Results: Between December 14th 2012 and July 15th 2016, 264 consecutive patients had an extracranial stage III NSCLC based on FDG-PET. 111 out of these 264 patients (42.0%) were excluded because of no dedicated brain CE-CT (51.4%) had only a low dose CT for attenuation correction, 54 (68.6%) had a CE-CT but without dedicated brain imaging protocol). Forty (26.0%) of the remaining 153 patients were excluded because of asymptomatic brain metastases on dedicated CE-CT brain (N=8), second primary (N=6) or no brain MRI (N=26). 113 stage III patients were included (updated results of 118 patients will be presented). 57.5% of the included patients were male; mean age was 67.0 years, 84.1% had WHO ≤80. 60.2% had stage IIA (before MRI brain) and 42.5% had an adenocarcinoma. Median time (range) between FDG-PET-CE-CT and MRI was 2.0 (0.0-8.1) weeks. 5/112 (4.4%) patients had a solitary brain metastasis on MRI despite no suspect brain lesions on CE-CT. In retrospect, in one of these five patients a solitary brain metastasis could be identified on the 18FDG-PET-CE-CT scan. Conclusion: Although asymptomatic brain metastases were detected in staging CE-CT, MRI brain is in daily practice clinically relevant superior to a CE-CT in screening for brain metastases in stage III NSCLC.

Keywords: MRI versus CT, NSCLC, brain metastases, Screening

MA06.06 TUMOR MICROENVIRONMENT AND BRAIN METASTASES IN COMPLETELY RESECTED STAGE IIIA(N2) NON-SMALL CELL LUNG CANCER
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Background: Tumour-infiltrating lymphocytes (TILs) and tumor budding were all the markers of tumor microenvironment. This study aimed to explore the potential association of tumor microenvironment with brain metastases (BM) in patients with completely resected stage IIIA(N2) NSCLC. Methods: 301 consecutive patients with pathological stage IIIA(N2) NSCLC who underwent complete surgery were reviewed between January 2005 and July 2012. Full-face hematoxylin and eosin-stained sections from surgical specimens for each case were evaluated for the density of TILs. Patients were stratified into TIL and non-TIL groups based on pathological evaluation. Tumor budding was defined as single cancer cells and clusters composed of up to four cancer cells. According to the number of tumor budding per field, the cases were classified into two groups: grade 1, up to five budding foci; and grade 2, six or more budding foci. The relationship between tumor microenvironment and BM at the initial presentation was analyzed. Results: Brain was the most common site of distant failure, and 92.5% BM developed in 3 years after the complete resection. 53 (17.6%) patients had BM as the first failure. However, univariate analysis showed that TIL was not significantly associated with an increased risk of developing BM as the first site of failure in 3 years (P=0.196), a higher density of TILs was associated with improved postoperative survival time (P=0.058). Patients with the tumor budding ≥5 experienced increased BM in 3 years versus patients with the tumor budding <5 (P=0.068). Multivariate analysis showed that adenocarcinomas and multiple N2 stations were significantly associated with the high risk of BM as the initial site of failure in 3 years.

Keywords: Tumor Budding, brain metastases, stage IIIA(N2) NSCLC, tumor-infiltrating lymphocytes

MA06.07 IMPACT OF TYPE 2 DIABETES MELLITUS AND ITS METABOLIC CONTROL ON PROGNOSIS OF UNRESECTABLE NON-SMALL CELL LUNG CANCER PATIENTS
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Background: Type 2 Diabetes Mellitus (T2DM) has been associated with an increased risk of relapse and mortality in several cancer locations, but the prognostic value of T2DM or its metabolic control (MC) in patients (pts) with stage III non-small cell lung cancer (NSCLC) have not been studied yet. The purpose of this study is to evaluate the influence of T2DM and its MC on the prognosis of pts with NSCLC treated with concurrent chemoradiotherapy.
MAO6.09 EFFICACY RENO STUDY RESULTS OF ORAL VINORELBE OR ETOPSIDES WITH CISPLATIN & CHEMO-RADIATION IN STAGE III NSCLC.

SLGC 10/02

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Background: Concurrent chemoradiotherapy (CRT) is the standard treatment (TTR) for stage III NSCLC. Elderly patients (pts) are common, may have increased toxicity, & are under-represented in CRT trials. We performed a pooled analysis of IDCTN patient data (IDCTN) from phase 2/3 CRT trials of stage III NSCLC from 1990-2012 was collected. We compared the overall survival (OS), progression-free survival (PFS), & adverse events (AE's) for pts age ≥70 yrs (elderly) vs. <70yrs (younger). Unadjusted & adjusted Hazard Ratios (HR) for survival time & their confidence intervals (CI) were estimated by single-predictor & multivariable Cox models. Unadjusted & adjusted Odds Ratio (OR) for AE's & their CIs were obtained from single-predictor & multivariable logistic regression models. Results: IDCTN from 16 trials were analyzed, 2,768 pts were younger & 832 were elderly. Median OS & PFS for elderly vs younger pts are in the table. In the unadjusted & multivariable models elderly pts had worse OS (HR=1.23, 95%CI=1.13-1.35, and 1.20, 95%CI=1.01-1.32, respectively). In the unadjusted & multivariable models, elderly & younger pts had a similar PFS (HR=1.02; 95%CI=0.94-1.11 and 1.01, 95%CI=0.92-1.10, respectively). Elderly pts had a higher rate of grade 3 AEs in the unadjusted & multivariable models (OR=2.5; 95%CI=1.00-5.17 and 1.30; 95%CI=1.03-1.62, respectively). A lower percentage of elderly pts compared to younger completed TTR (47% and 57%, respectively; P=0.001) & higher percentage stopped due to AE’s (20% and 13%, P<0.0001). Grade ≥3 AEs (occurring at a rate ≥2.5%) with a higher rate in the elderly: neutropenia, dyspnea, fatigue, anorexia, vomiting, dehydration, hypoxia, hypotension, & pneumonitis (P<0.05).

Background: Concurrent chemoradiotherapy (CRT) is the standard treatment (TTR) for stage III NSCLC. Elderly patients (pts) are common, may have increased toxicity, & are under-represented in CRT trials. We performed a pooled analysis of IDCTN patient data (IDCTN) from phase 2/3 CRT trials of stage III NSCLC from 1990-2012 was collected. We compared the overall survival (OS), progression-free survival (PFS), & adverse events (AE's) for pts age ≥70 yrs (elderly) vs. <70yrs (younger). Unadjusted & adjusted Hazard Ratios (HR) for survival time & their confidence intervals (CI) were estimated by single-predictor & multivariable Cox models. Unadjusted & adjusted Odds Ratio (OR) for AE's & their CIs were obtained from single-predictor & multivariable logistic regression models. Results: IDCTN from 16 trials were analyzed, 2,768 pts were younger & 832 were elderly. Median OS & PFS for elderly vs younger pts are in the table. In the unadjusted & multivariable models elderly pts had worse OS (HR=1.23, 95%CI=1.13-1.35, and 1.20, 95%CI=1.01-1.32, respectively). In the unadjusted & multivariable models, elderly & younger pts had a similar PFS (HR=1.02; 95%CI=0.94-1.11 and 1.01, 95%CI=0.92-1.10, respectively). Elderly pts had a higher rate of grade 3 AEs in the unadjusted & multivariable models (OR=2.5; 95%CI=1.00-5.17 and 1.30; 95%CI=1.03-1.62, respectively). A lower percentage of elderly pts compared to younger completed TTR (47% and 57%, respectively; P=0.001) & higher percentage stopped due to AE’s (20% and 13%, P<0.0001). Grade ≥3 AEs (occurring at a rate ≥2.5%) with a higher rate in the elderly: neutropenia, dyspnea, fatigue, anorexia, vomiting, dehydration, hypoxia, hypotension, & pneumonitis (P<0.05).
MA06.11 PHASE II STUDY OF NIMOTUZUMAB + CONCURRENT CHEMORADIOTHERAPY (CRT) FOR STAGE III NON SMALL CELL LUNG CANCER (NSCLC): 5-YEAR FOLLOW-UP RESULTS
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Background: Nimotuzumab, a humanized IgG, monoclonal anti-EGFR antibody, is approved and widely used in patients (pts) with head and neck cancer or malignant glioma in combination with radiotherapy (RT) in several countries. In vitro and in vivo experiments using NSCLC cell lines, nimotuzumab showed a radio-sensitizing effect. Methods: This phase II study evaluated the tolerability and efficacy of nimotuzumab in combination with concurrent CRT in pts with unresectable locally advanced NSCLC. All eligible pts received concurrent thoracic RT (60 Gy) divided into 2 Gy/day, 6 weeks from day 1 and 4 cycles of chemotherapy (cisplatin 80 mg/m² on day 1, vinorelbine 20 mg/m² on days 1 and 8) once every 4 weeks as scheduled. Nimotuzumab (200 mg) was administered once a week from cycle 1 to 4. The primary endpoint was tolerability in combination with concurrent CRT, which was measured by the percentage of pts who completed 60 Gy of RT within 8 weeks, completed 2 cycles of chemotherapy and received more than 75% of nimotuzumab.

Results: Of 40 pts enrolled between June 2009 and May 2010, 39 eligible pts received the study treatment. The pts characteristics were as follows: 62 years (median, male/female, 34/5, stage IIA/B, 21/18, PS 0/1, 25/14. Thirty-four pts met the criteria for treatment tolerability, and 38 pts completed 2 cycles of nimotuzumab and RT within 8 weeks. Infusion reaction, grade 3 skin rash, grade 3 radiation pneumonitis, or grade 4 hematological toxicity were not observed. The 3-year and 5-year overall survival rates for the 39 pts were 66.4% and 58.4%, respectively. The median PFS was 16.9 months, and the 5-year PFS rate for pts with squamous cell carcinoma (Sq, n = 16) was 50.0%, while for pts with non-squamous cell carcinoma (non-Sq, n = 23) was 13.7%. In terms of the first relapse site, in-field relapse rates were low for both Sq (4/16, 25%) and non-Sq (4/23, 17%). However, the distant relapse rate was significantly higher for non-Sq patients than that for Sq patients. Cytologic or histologic specimens were examined for the expression of EGFR protein/mutations using the EGFR IHC/FISH methods in 20 pts. Nimotuzumab showed a radio-sensitizing effect.

Elderly pts in CCRT trials had worse outcomes (older than 70 years, 14/23 patients; 30.4% of overall population). Seventy percent of patients had prior CNS radiotherapy; 58% of these completed radiotherapy >6 months before study entry. Updated CNS data are shown in the Table and are consistent with systemic results.

Keywords: Chemoradiotherapy, locally advanced non-small cell lung cancer, nimotuzumab, molecular targeting drug.
MA07.05 EUCROSS: A EUROPEAN PHASE II TRIAL OF CRIZOTINIB IN ADVANCED ADENOCARCINOMA OF THE LUNG HARBORING ROS1 REARRANGEMENTS - PRELIMINARY RESULTS

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Background: ROS1 rearrangements are present in the tumors of 1-2% of patients with lung adenocarcinoma (LADC). This patient subgroup is characterized by non-smoking history and younger than average age compared to the overall NSCLC population. In a phase I trial the ALK/Ros1 inhibitor crizotinib has shown to be highly effective in these patients (NCT00585195). EUCROSS is a prospective phase II trial of the Lung Cancer Group Cologne in collaboration with the Spanish Lung Cancer Group to evaluate crizotinib in ROS1-positive LADC. Here, we present preliminary data on efficacy and safety. Methods: Patients with advanced LADC harboring ROS1 rearrangements as confirmed by central FISH were eligible for the trial irrespective of the number of prior treatment lines. Patients received treatment with crizotinib 250 mg BID - doses were adapted for management based on efficacy. The release of study data because the superiority in PFS had been demonstrated for ALK based on second IA. The PFS HR of ALK arm to CR arm was 0.34 (99.6826% CI: 0.17-0.70, stratified log-rank p < 0.001). Median PFS was not reached (95% CI: 20.3-Not Reached (NR)) in ALK arm while it was 10.2 months (95%CI: 8.2-12.0) in CR arm. ALK demonstrated favorable result of PFS in each sub-group for instance, treatment line (1st line: HR = 0.30, ALK vs CR: 10.2 months, 2nd line: HR = 0.39, ALK: 20.3 months vs CR: 8.2 months), brain metastases at baseline (yes: HR = 0.08, ALK: NR vs CR: 10.2 months, no: HR = 0.39, ALK: 20.3 months vs CR: 10.0 months) and clinical stage (stage IIIb/IV: HR = 0.31, ALK: 20.3 months vs CR: 8.3 months, recurrence: HR > 0.60, ALK: NR vs CR: 11.6 months). Grade 3-4 AEs (ALK: 26% vs CR: 52%), discontinuation of study drug due to AEs (ALK: 9% vs CR: 20%) and dose interruptions due to AEs (ALK: 29% vs CR: 74%) occurred with lower rate in the ALK arm. There were no treatment-related deaths in either arm up to now. Overall survival (OS) was analyzed by DNA-sequencing to identify the translocation partners of ROS1. A total of 16 patients were enrolled. Patients received oral crizotinib (67.4,88.1)‡ n=16 12§ n (%) PD, n (%) Missing/NE, n (%) DCR, safety.

Keywords: ALK Inhibitor, ALK+ NSCLC

MA07.03 ALECTINIB (ALC) VERSUS CRIZOTINIB (CRZ) IN ALK-INHIBITOR NAIVE NSCLC: PRIMARY RESULTS FROM PHASE III STUDY (J-ALEX)

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Background: Alk inhibitors are the standard treatment for ALK+ NSCLC and the comparison between 2 ALK inhibitors will be valuable in determining therapeutic strategy for ALK+ NSCLC patients (pts). We conducted the randomized open-label Phase III trial designed to prove the superior PFS of ALC to CRZ in ALK-inhibitor naïve NSCLC. Methods: ALK+ NSCLC pts were randomized 1:1 either to receive ALC (300 mg b.i.d) or CRZ (250 mg b.i.d) and stratified by ECOG PS (0/1 vs 2), treatment line (1st vs 2nd), and clinical stage (IIIB/IV vs recurrence). Primary endpoint was PFS according to the blinded independent review board. Secondary endpoints included overall survival, objective response rate, and safety. Under an assumption of hazard ratio (HR) of 0.643, 164 events were required to have 80% power with 2-sided alpha of 0.05. Three interim analyses (IA) for early stopping due to efficacy were planned after 33%, 50%, and 75% of required PFS events occurred. Results: 207 pts were enrolled at 41 centers in Japan between November 2013 and August 2015. Independent data monitoring committee recommended the release of study data because the superiority in PFS had been demonstrated for ALK based on second IA. The PFS HR of ALC arm to CRZ arm was 0.34 (99.6826% CI: 0.17-0.70, stratified log-rank p < 0.001). Median PFS was not reached (95% CI: 20.3-Not Reached (NR)) in ALC arm while it was 10.2 months (95%CI: 8.2-12.0) in CR arm. ALC demonstrated favorable result of PFS in each sub-group for instance, treatment line (1st line: HR = 0.30, ALC vs CRZ: 10.2 months, 2nd: line: HR = 0.39, ALC: 20.3 months vs CRZ: 8.2 months), brain metastases at baseline (yes: HR = 0.08, ALC: NR vs CRZ: 10.2 months, no: HR = 0.39, ALC: 20.3 months vs CRZ: 10.0 months) and clinical stage (stage IIIB/IV: HR = 0.31, ALC: 20.3 months vs CRZ: 8.3 months, recurrence: HR > 0.60, ALC: NR vs CRZ: 11.6 months). Grade 3-4 AEs (ALK: 26% vs CRZ: 52%), discontinuation of study drug due to AEs (ALK: 9% vs CRZ: 20%) and dose interruptions due to AEs (ALK: 29% vs CRZ: 74%) occurred with lower rate in the ALC arm. There were no treatment-related deaths in either arm up to now. Overall survival (OS) was analyzed by DNA-sequencing to identify the translocation partners of ROS1. A total of 16 patients were enrolled. Patients received oral crizotinib (67.4,88.1)‡ n=16 12§ n (%) PD, n (%) Missing/NE, n (%) DCR, safety.

Keywords: ALK Inhibitor, ALK+ NSCLC

MA07.03 ALECTINIB (ALC) VERSUS CRIZOTINIB (CRZ) IN ALK-INHIBITOR NAIVE NSCLC: PRIMARY RESULTS FROM PHASE III STUDY (J-ALEX)

TUESDAY, DECEMBER 6, 2016 - 11:00-12:30
Results: In total, 34 patients were enrolled in EURCROSS at the time of data cut-off. Twenty-nine patients were eligible for efficacy assessment. Tumor tissue of 20 of these patients was suitable for further sequencing. 18 were sequenced positive for ROS1 fusion. The fusion partners involved were CD74 (N=9,550%), EZR (N=4,22%), SLC34A2 (N=3,16%), TPM3 and SDCC4(N=1,6%) each. The investigator assessed ORR was 69% (95% CI, 49.1-83.4) in the overall trial population and 83% (95% CI, 67.7-94.2) in the ROS1-positive by sequencing population (N=18; P=0.324 for difference of ORR). Three patients (N=3,95%, 3.6-26.4) exhibited primary progression, two of them were sequenced ROS1-negative. All patients were included in the safety population (N=34). Most common AEs irrespective of relatedness or grade were visual disorders (N=16,48%), edema (N=14,41%), diarrea (N=13,38%) and bradycardia (N=17,32%). Conclusion: Crizotinib is a highly effective and safe treatment in the subset of ROS1 rearranged NSCLC patients. As endpoints are determination by FISH and DNA-sequencing. Although, the number of patients with tissue available for sequencing was low at the time of data cut-off, sensitivity and specificity support the potential as a non-standard gold-standard for the identification of clinically relevant ROS1 gene rearrangements.

Keywords: NSCLC, crizotinib, ROS1

MA07.06 CRIZOTINIB IN ROS1 REARRANGED OR MET DEREGERULATED NON-SMALL-CELL LUNG CANCER (NSCLC): PRELIMINARY RESULTS OF THE METROS TRIAL

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Background: Crizotinib is an orally active inhibitor of receptor tyrosine kinase fusions in NSCLC with ALK rearrangement. Recent data showed that this agent is dramatically effective in patients with ALK+ disease, with 61% (95% CI, 49-75%) ORR and 50% (95% CI, 36-63%) median progression-free survival in the first-line setting. Crizotinib demonstrated potent clinical activity in patients with advanced, ALK+ NSCLC, who received at least one prior line of chemotherapye. Of 5 patients with retrospectively confirmed brain metastases, 4 (80%) had an objective response. The median progression-free survival was 19.3 months (95% CI, 7.2-not reached), with 17 (53%) patients still in follow-up for progression. The median overall survival was not reached at the time of the data cut-off. Of the 32 patients enrolled, 28 patients were evaluable for response by independent radiologic review. The median duration of response was 10.0 months (range, 0.4–18.4). Among 11 tumors that were tested by FISH, we identified 7 EML4-ALK fusion partners (N=6; 58%), ROS1-SLC34A2 (N=1; 9%) and ROS1-ERZ. The median progression-free survival was 19.3 months (95% CI, 7.2-not reached), with 17 (53%) patients still in follow-up for progression. The median overall survival was not reached at the time of the data cut-off. Of 51 patients with retrospectively confirmed brain metastases, intracranial disease control was reported in 4 patients (80%). Gastrointestinal adverse events (vomiting, nausea, diarrhea) mostly grade 1-2, were the most frequent adverse events (80%); these events were manageable. Conclusion: Crizotinib demonstrated potent clinical activity in patients with advanced, ROS1-rearranged NSCLC, who received at least one prior line of platinum-based chemotherapye. ROS1 fusion partners were identified in 58% of the patients with this subgroup of NSCLC for which crizotinib is highly active (ClinicalTrials.gov number, NCT01964157).

Keywords: Non-small-cell lung cancer, Crizotinib, ROS1

MA07.09 MASS SPECTROMETRY PROFILING AND IMAGING PLATFORM FOR NOVEL PRECISION DRUG RESISTANCE BIOMARKERS DISCOVERY IN EML4-ALK LUNG ADENOCARCINOMA

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Background: ROS1 rearrangement is a distinct molecular subset of non-small-cell lung cancer (NSCLC). We investigated the efficacy and safety of ceritinib in patients with ROS1-rearranged NSCLC. Methods: We enrolled 32 patients with advanced NSCLC who tested positive for ROS1 rearrangement by fluorescent in situ hybridization (FISH). ROS1 immunohistochemistry (IHC) and next-generation sequencing (NGS) was performed in available tumor samples. Ceritinib 750mg was administered once daily and the primary endpoint was objective response rate (ORR) by central independent radiologic review. The secondary endpoints included disease control rate (DCR), duration of response, progression-free survival (PFS), overall survival (OS), toxicity and comparison between FISH and NGS results. Results: Between June 7, 2013, and February 1, 2016, a total of 404 patients underwent ROSI prescreening, and 32 ROS1+ (by FISH) patients were enrolled. All patients except two (who did not respond to ceritinib) were ceritinib naive. The median age of all patients was 62 years, and there were 24 females (75%). The majority of patients (84%) were never smokers, and all had adenocarcinoma histology. The median number of previous treatments before study enrollment was 3 (range, 2-7) and 17 (53%) patients had received three or more lines of chemotherapy. At the time of the data cut-off (April 18, 2016), the median follow-up was 7.5 months, and 15 (47%) patients had discontinued treatment. Of the 32 patients enrolled, 28 patients were evaluable for response by independent radiologic review. ORR was 63% (95% CI, 45-77.9%), with 1 complete response and 19 partial responses. The median duration of response was 10.0 months (range, 0.4–18.4). Among 11 tumors that were tested by NGS, we identified 7 EML4-ALK fusion partners (N=6; 58%), ROS1-SLC34A2 (N=1; 9%) and ROS1-ERZ. The median progression-free survival was 19.3 months (95% CI, 7.2-not reached), with 17 (53%) patients still in follow-up for progression. The median overall survival was not reached at the time of the data cut-off. Of 51 patients with retrospectively confirmed brain metastases, intracranial disease control was reported in 4 patients (80%). Gastrointestinal adverse events (vomiting, nausea, diarrhea) mostly grade 1-2, were the most frequent adverse events (80%); these events were manageable. Conclusion: Ceritinib demonstrated potent clinical activity in patients with advanced, ROS1-rearranged NSCLC, who received at least one prior line of platinum-based chemotherapy. ROS1 fusion partners were identified in 58% of the patients with this subgroup of NSCLC for which ceritinib is highly active (ClinicalTrials.gov number, NCT01964157).

Keywords: Non-small-cell lung cancer, Ceritinib, ROS1

MA07.07 CERTINIB IN ROS1-REARRANGED NON-SMALL-CELL LUNG CANCER: AN UPDATE OF KOREAN NATIONALWIDE PHASE II STUDY

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profiles between control tumors and 7- and 14-day ALK+ treated tumors using a histology guided mass spectrometry approach. Additionally, frozen control and ALK+ treated tumors were subjected to full section MSI to determine the 46-kb drug distribution as well as the changing landscape of lipids and metabolites. In parallel, Ma-ALK001.S cell line was treated with alectinib (ALK-i) in culture with samples collected at 0 hr, 8 hr, 3 days, 7 days, and 14 days. Cells were subjected to both MALDI-MS profiling analysis and Laser Ablation Electrospray Ionization (LAESI)-MS analysis. Statistical analyses were performed using Markerlynx and SCiLS. Results: ALK+ H3122 lung adenocarcinoma murine xenograft model in vivo under treatment with/ without ALK+ 1A6E84 was used in MSI studies at treatment day 0, 7 day and 14 day, during tumor response. Pairwise and 3-way Wilcoxon rank sum tests were carried out and a Bonferroni correction applied. The greatest number of significantly altered peaks were observed between day 0 and day 14 (67%). Pairwise linear discriminant analysis classification algorithm models were generated resulting in over 94% classification accuracy in all comparison. Direct MS/MS fragmentation revealed that ALK+ was detected within the frozen ALK+ tumors in early drug-escape. Several lipids were identified to expression landscape changes emerging under ALK+ i. Biomolecular (peptides, lipids, and metabolites) profiling of Ma-ALK001.S cell line using combined MALDI and LAESI MSI analysis was successful, which provided novel insights into the early mechanisms of molecular drug resistance emergence. Conclusion: MSI allowed for direct in situ determination of the evolving expression landscape of biomolecules in ALK+ lung cancer under ALK+ i precision therapy. These results provide a rationale to advance our MSI profiling studies for biomarkers discovery to gain deeper insights into molecular mechanisms of adaptive precision drug resistance emergence.

Keywords: drug resistance, mass spectrometry, ALK rearranged lung cancer, Precision therapy

MA07. ALK+NSCLC TUESDAY, DECEMBER 6, 2016 - 11:00-12:30

MA07.10 HDAC INHIBITION OVERCOMES CRIZOTINIB-RESISTANCE BY INDUCING METAMERIC EPITHELIAL TRANSITION (MET) IN EML4-ALK LUNG CANCER

Koji Fukuda, Shinji Takeuchi, Ryohio Katayama, Shigeki Nanjo, Tadaaki Yamada, Takeshi Suzuki, Kengo Takeuchi, Makoto Nishio, Seiji Yano

Background: ALK rearrangement, most commonly EML4-ALK, is detected in approximately 3–7% of non-small cell lung cancer (NSCLC). Crizotinib, an ALK tyrosine kinase inhibitor (TKI), shows dramatic clinical efficacy in ALK-rearranged NSCLC patients. However, almost all patients acquire resistance after only 1 to 2 years. A variety of mechanisms, including ALK-secondary mutations, ALK amplification, and activation of alternative pathway, have been reported to mediate acquired resistance to crizotinib. While epithelial-mesenchymal transition (EMT) was recently reported to be associated with resistance to crizotinib in EML4-ALK lung cancer cells in vitro, the underlying mechanism has not been defined and no optimal therapy to overcome EMT-associated resistance has been identified. Methods: We continuously gave crizotinib treatment to SCID mice inoculated with EML4-ALK lung cancer cell line A925L into thoracic cavity and established crizotinib resistant A925L cells. After the limiting dilution of A925L cells, we obtained several single cell clones. The effects of the HDAC inhibitor quisinostat on the EMT state and the growth of the cells were examined in vitro and in vivo. Results: We found that some clones acquired EMT phenotypes, such as spindle shape morphology, expression of EMT-related proteins, and increased cell motility. Interestingly, Histone deacetylase (HDAC) inhibitor, quisinostat, induced mesenchymal-epithelial transition (MET) of A925L cells. Quisinostat induced MET, induced restoration sensitivity to crizotinib. Knockdown of ZEB1 expression in the A925L cells by si-RNA also induced MET and restored sensitivity to crizotinib, suggesting that quisinostat-induced MET depends on ZEB1 suppression. MicroRNA profile analysis revealed that the A925L cells expressed significantly lower levels of mir-200 family including mir-200c which targets ZEB1, compared with parental A925L cells. Furthermore, quisinostat recovered mir-200 expression and antago-mir-200c abrogated quisinostat-induced MET in the A925L cell clones. These results indicate that quisinostat induced MET by up-regulating mir-200c expression which target ZEB1 and thereby re-establishing to crizotinib. In a pleural carcinomatosis model with A925L CR clone cells, quisinostat induced MET and caused remarkable tumor regression during the subsequent crizotinib re-challenge. Furthermore, we analyzed tumor tissue obtained at autopsy from an ALK-rearranged NSCLC patient who acquired resistance to crizotinib. We found that EMT was induced in both primary and metastasis lesions after crizotinib treatment, indicating that EMT is associated with crizotinib resistance in clinical therapy. Conclusion: Our findings suggest that EMT is possibly occurred in acquired resistance to crizotinib and intermittent use of HDAC inhibitor could be a novel therapeutic strategy for overcoming EMT-associated crizotinib-resistance in EML4-ALK lung cancer.

Keywords: mir-200, EML4-ALK, EMT, HDAC inhibitor

MA07. ALK+NSCLC TUESDAY, DECEMBER 6, 2016 - 11:00-12:30

MA07.11 SAFETY AND EFFICACY OF LORlatinib (PF-06463922) IN PATIENTS WITH ADVANCED ALK+ OR ROS1+ NON-CELL LUNG CANCER (NSCLC)

E Felip, T Bauer, Benjamin Solomon, B Besse, L James, J Clancy, K Klamerus, J-F Martini, A Abbattista, A Shaw

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Background: Patients with anaplastic lymphoma kinase (ALK) and c-ros oncogene 1 (ROS1) NSCLC often become resistant to tyrosine kinase inhibitor (TKI) therapy; central nervous system (CNS) relapse is common. Lorlatinib is a selective brain-penetrant ALK/ROSI TKI, active against most known resistance mutations. Methods: In Ph I of the ongoing Ph II study NCT01970865, patients had ALK+ or ROSI+ NSCLC + brain metastases and were treatment naive or had disease progression after ≥2 TKIs. Patients received lorlatinib on day –7 and then once or twice daily from day 1. Primary objective was identification of MTD and recommended Ph II dose (RP2D). Other objectives were safety and efficacy by RECIST v1 including intracranial activity. Results: Of 54 patients treated in Ph I (cutoff Jan 15, 2016), 41 were ALK+ 1 ROSI+, and 1 had mutation status unconfirmed for ALK+ or ROSI+. Patients were heavily pretreated: 27 had received ≥2 prior TKIs and 20 had ≥1 prior TKI. 39 patients had CNS metastases at baseline. Patients were treated across 10 dose levels (total daily dose of 10–200 mg). Response rates were...
SESSION MA08: TREATMENT MONITORING IN ADVANCED NSCLC TUESDAY, DECEMBER 6, 2016 - 11:00-12:30

MA08.01 A HIGHLY SENSITIVE NEXT-GENERATION SEQUENCING PLATFORM FOR DETECTION OF NSCLC EGFR T790M MUTATION IN URINE AND PLASMA

Heather Wakelee, Vlada Melnikova, Chris Karlovich, Shirish Gadgeel, Karen Reckamp, Jonathan W. Goldman, D. Ross Camidge, Maurice Péro, Sai-Hong Ou, Stephen Liu, Helen Yu, Mark Socinski, Tarek Mekhail, Benjamin Solomon, Ronald Natale, Gregory Otterbert, Vassiliki Papadimitrakopoulou, Jean-Charles Soria, Cory Langer, Joel Neal, Darin Despain, Sergey Yusov, Jason Litten, Mitch Rapoza, Mark Erlander, Leicu Sescut(1)

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Background: Non-invasive genotyping of NSCLC patients by circulating tumor DNA (ctDNA) is a promising alternative to tissue biopsies. However, ctDNA EGFR mutation analysis remains challenging in patients with intrathoracic disease, with a reported 26%-57% T790M mutation detection rate in plasma (Karlovich et al., ASCO 2016). We investigated whether a mutation enrichment NGS test could improve mutation detection in plasma and urine from T790M+ patients who had negative results in previous testing in patients with EGFR mutation-positive advanced NSCLC.

Methods: The Therascreen (Qiagen) or cobas (Roche) EGFR test was used for EGFR T790M analysis in tumor biopsies. Urine and plasma were analyzed by next-generation sequencing (NGS) using the Ion 170 and 1770 T790M positive case datasets. The test was concordant for T790M+ and − in 192 (81.6%) and 179 (79.9%) of T790M+ and − urine, respectively. Of 25 cases positive by ctDNA but negative/inadequate by tissue, 16 were double-positive in plasma and urine, unlike to be false positive (Figure 1). T790M detection rate was higher for extrathoracic (n=119) vs intrathoracic (n=55) disease in plasma (87.4% vs 69.1%, p=0.006) but not urine (81.5% vs 76.4%, p=0.42). Combination of urine and plasma identified 179 T790M+ patients (92.7% of intrathoracic and 95.8% of extrathoracic cases (p=0.47). In 179 T790M+ patients, objective response rate was similar whether mutation was identified by tissue, plasma or urine (37.4%, 33% and 36%, respectively, in 4 patients T790M+ by urine but negative by tissue responded, and 2 of 8 patients T790M+ by plasma but negative by tissue responded. Conclusion: Mutation enrichment NGS testing by urine and plasma combined identified 94.8% of T790M+ cases.

Keywords: liquid biopsy, NSCLC, EGFR T790M, urine

MA08.02 CLINICAL RESEARCH PLATFORM INTO MOLECULAR TESTING, TREATMENT, OUTCOME (CRISP): A PROSPECTIVE

GERMAN REGISTRY IN STAGE IV NSCLC AIO-TRK-0315

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Background: Treatment in non-small cell lung cancer is quickly evolving and new agents make it to the routine practice at a rapid pace. Whether outcome and PRO data generated in clinical trials with often narrow exclusion and inclusion criteria will hold up in the routine practice is of high interest, especially due to the increasing costs of new drugs. Therefore registry data are of ever increasing importance to patients, physicians and reimbursement institution.

Methods: Therefore, we have started a prospective, clinical registry for patients with metastatic non-small cell lung cancer. The purpose of CRISP is to set up a national clinical research platform to document representative data on molecular testing, sequences of systemic therapies and other treatment modalities, course of disease in patients with advanced or metastatic NSCLC in Germany not amenable to curative treatments. In particular focus is on molecular biomarker testing of patients before the start of first-line treatment. The data shall be used to assess the current state of care and to develop recommendations concerning topics that could be improved. PRO assessment will provide large-scale data on quality of life and anxiety/depression for real-life German patients. In addition, two questionnaires (concerning individual quality of life and patient-caregiver communication) will be validated in German patients with metastatic NSCLC. Furthermore CRISP will set up a decentral tissue annotation for future collaborative, investigational scientific biomarker testing.

Results: This study will be carried out in up to 150 representative cancer centers in all therapeutic sectors in Germany. More than 8000 patients will be recruited and followed up to a maximum of 3 years, respectively until death. The first patients have been included as of December 2015. As of yet, 82 centers have been initiated, 211 patients have been recruited. Preliminary data will be presented at the meeting in terms of molecular test results, demographic data as well as treatment stratification in the 1st line setting. Conclusion: The registry CRISP will be the first to present representative real life data, covering all treatment settings of patients with NSCLC in Germany. Clinical Trials.gov Identifier: NCT02222581 CRISP is supported by GlaxoSmithKline, Boehringer Ingelheim Pharma GmbH & Co. KG, Bristol-Myers Squibb GmbH & Co. KGaA, Celgene GmbH, MSD Sharp & Dohme GmbH, Novartis Pharma GmbH, and Pfizer Pharma GmbH.

Keywords: NSCLC, molecular testing

MA08.03 OSIMERTINIB VS PLATINUM-PERMETREXED FOR T790M-MUTATION POSITIVE ADVANCED NSCLC (AURA3): PLASMA CTDNA ANALYSIS

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Background: AURA3 (NCT02151981) is a Phase III, open-label, randomised study assessing the efficacy and safety of osimertinib, a T790M directed EGFR-TKI, vs platinum-based doublet chemotherapy in patients with EGFR T790M positive advanced NSCLC, whose tumours progressed on previous EGFR-TKI therapy. Concordance between plasma and tissue testing, and efficacy outcomes by baseline plasma T790M status, were evaluated.

Keywords: liquid biopsy, NSCLC, EGFR T790M, urine
Methods: Eligible patients were randomised 2:1 to osimertinib 80 mg orally once daily or platinum-pemetrexed (pemetrexed 500 mg/m² + cisplatin 75 mg/m² or carboplatin AUC5) every three weeks for up to six cycles. Patients were tumour tissue T790M-positive (by cobas® EGFR Mutation Test v2) from a biopsy after disease progression prior to study entry. Blood samples were taken at baseline for retrospective analysis of T790M mutation status by plasma ctDNA using the cobas® EGFR Mutation Test v2. Results: Concordance data are reported in the table. Within the intent-to-treat (ITT) population (n=419), patients plasma T790M-positive and randomised to treatment (n=172) had markedly improved progression-free survival (PFS) by investigator assessment (IA) with osimertinib vs platinum-pemetrexed: hazard ratio 0.42 (95% CI: 0.29, 0.61); median 8.2 vs 4.2 months. Objective response rate (ORR) was 71% vs 31% (odds ratio 5.39 [95% CI: 3.47, 8.48]; p<0.001). This is consistent with the ITT population: PFS hazard ratio 0.30 (95% CI: 0.23, 0.41); p=0.001 (median 10.1 vs 4.4 months); ORR 71% vs 31% (odds ratio 5.93 [95% CI: 3.47, 8.48]; p<0.001).

Conclusion: In plasma T790M-positive patients the clinical benefit of osimertinib was superior to platinum-pemetrexed, consistent with the ITT T790M-positive population selected by tumour tissue test. PFS with osimertinib was superior to platinum-pemetrexed, consistent with the AURA Phase II data, and was clinically meaningful. This exploratory analysis confirmed the findings from our previous report where patients with T790M-positive status based on plasma ctDNA using the cobas® EGFR Mutation Test v2 had markedly improved progression-free survival compared with patients with T790M-negative status.

Keywords: plasma testing, osimertinib, EGFR mutation-positive NSCLC

MA08: TREATMENT MONITORING IN ADVANCED NSCLC
TUESDAY, DECEMBER 6, 2016 - 11:00-12:30

MA08:05 DEPTH OF RESPONSE TO FIRST-LINE EGFR TKI DOES NOT PREDICT SURVIVAL IN EGFR-MUTATED NSCLC PATIENTS
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Background: The association between depth of response to EGFR TKI and prognosis of EGFR-mutated NSCLC remains unclear. We aimed to assess the correlation between maximal tumor shrinkage and survival in patients treated with gefitinib and afatinib. Methods: Patients with advanced EGFR-mutated NSCLC enrolled in first-line gefitinib and afatinib clinical trials between 2005 and 2014 at the National Taiwan University Hospital were reviewed. Patients who had at least one measurable target lesion that shrank during treatment were included. Overall survival (OS) was defined as time from date of enrollment to death or May 30, 2016. The 95th percentile of the marginal survival curve at 24 months for each quartile was calculated using the Kaplan-Meier method. The influence of high maximal tumor shrinkage (≥75%) on OS was analyzed by Pearson correlation coefficient and multivariate analysis with age and gender as covariates. Results: A total of 189 trial patients were screened and 91 patients were eligible for analysis (gefitinib n=42, afatinib n=49). The median maximal tumor shrinkage during first-line EGFR TKI treatment was 53% (interquartile range 30.5%). Maximal tumor shrinkage did not correlate with OS in all patients (R²=0.0225, p=0.169). Conclusion: DpR, defined as maximum tumor shrinkage, has emerged as a potential predictor for long-term treatment outcome across multiple tumors, including NSCLC treated with immunotherapy or targeted therapy. This exploratory analysis evaluated whether DpR correlated with survival in patients with advanced NSCLC treated with platinum-doublet chemotherapy in a phase III randomized clinical trial. Methods: Patients received first-line nab-paclitaxel 100 mg/m² weekly or paclitaxel 200 mg/m² qw2, both + carboplatin AUC6 qw3. The current analysis evaluated DpR as best percent change from baseline in total target lesion length during treatment. For patients with tumor shrinkage, data were grouped into quartiles based on maximum percent shrinkage from baseline (Q1: ≥0%–<25%, Q2: ≥25%–<50%; Q3: ≥50%–<75%, Q4: ≥75%) and compared with data from patients with no change or tumor growth (NC/G). Results: Tumor measurement by independent review (baseline and postbaseline) was evaluable in 959 patients pooled across treatments. The median (Figure) and 1-year OS increased with each quartile vs NC/G for age (P=0.0001, HR=3.06) and histology (squamous and nonsquamous) in subset analyses (P=0.05 for all comparisons). Conclusion: DpR was associated with increased OS in patients with advanced NSCLC receiving first-line platinum-based doublet chemotherapy, regardless of age or histology. These findings underscore the importance of evaluating quality of treatment response in this patient population.

Keywords: plasma testing, osimertinib, EGFR mutation-positive NSCLC

MA08.06 IMPACT OF DEPTH OF RESPONSE (DPR) ON SURVIVAL IN PATIENTS WITH ADVANCED NSCLC TREATED WITH FIRST-LINE CHEMOTHERAPY
Daniel Morgensztern1, Mary O’Brien2, Teng Ong3, Mark Socinski4, Pieter Postmus5, Amy Ko6
1Washington University School of Medicine in St. Louis, St. Louis/MO/United States of America, 2Royal Marsden Hospital, London/United Kingdom, 3Celgene Corporation, Summit/NJ/United States of America, 4Florida Hospital Cancer Institute, Orlando/FL/United States of America, 5Clatterbridge Cancer Center, Liverpool/United Kingdom

Background: DpR, defined as maximum tumor shrinkage, has emerged as a potential predictor for long-term treatment outcome across multiple tumors, including NSCLC treated with immunotherapy or targeted therapy. This exploratory analysis evaluated whether DpR correlated with survival in patients with advanced NSCLC treated with platinum-doublet chemotherapy in a phase III randomized clinical trial. Methods: Patients received first-line nab-paclitaxel 100 mg/m² weekly or paclitaxel 200 mg/m² qw2, both + carboplatin AUC6 qw3. The current analysis evaluated DpR as best percent change from baseline in total target lesion length during treatment. For patients with tumor shrinkage, data were grouped into quartiles based on maximum percent shrinkage from baseline (Q1: ≥0%–<25%, Q2: ≥25%–<50%; Q3: ≥50%–<75%, Q4: ≥75%) and compared with data from patients with no change or tumor growth (NC/G). Results: Tumor measurement by independent review (baseline and postbaseline) was evaluable in 959 patients pooled across treatments. The median (Figure) and 1-year OS increased with each quartile vs NC/G for age (P=0.0001, HR=3.06) and histology (squamous and nonsquamous) in subset analyses (P=0.05 for all comparisons). Conclusion: DpR was associated with increased OS in patients with advanced NSCLC receiving first-line platinum-based doublet chemotherapy, regardless of age or histology. These findings underscore the importance of evaluating quality of treatment response in this patient population.

Keywords: plasma testing, osimertinib, EGFR mutation-positive NSCLC

MA08: TREATMENT MONITORING IN ADVANCED NSCLC
TUESDAY, DECEMBER 6, 2016 - 11:00-12:30

MA08: TREATMENT MONITORING IN ADVANCED NSCLC
TUESDAY, DECEMBER 6, 2016 - 11:00-12:30
MA08.07 PROSPECTIVE SEQUENTIAL COUNTS OF TOTAL CTC OR CKIT-CTC IN ADVANCED NSCLC WITH 1ST LINE CHEMOTHERAPY (POLICE)
Yu-Chao Zhang1, Zhen Wang2, Yan-Ming Deng1, Wei-Bang Guo1, Jin-Ji Yang1, Hong-Hong Yan1, Qing Zhou1, Binhao Wang2, Wei-Neng Feng1, Huajuan Chen1, Hai-Yan Tu1, Li Zhang1, Xiaoqing Liu3, Qing-Feng Zou3, Yi Long Wu3
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Background: Circulating tumor cells (CTCs) have been reported to be prognostic and predictive in non-small cell lung cancer (NSCLC) and a few of other cancer types. In 1st line setting, whether EPCAM^+ CK^+ CD45^+ CTC enumeration and dynamic changes can be prognostic and/or predictive to standard chemotherapy need further investigation in Chinese patients with NSCLC. Methods: A prospective study on the CTC enumeration in advanced NSCLC with 1st line chemotherapy (POLICE) was started by China Thoracic Oncology Group (CTONG). Patients with NSCLC naïve for systemic regimens were enrolled since August 2013. CTCs were detected by Cell Search Platform and identified as positive for EPCAM^+ CK^+ CD45^+ phenotype. CD17^+ (KIT^+ marker) was added to test the frequency of stem cell-like KIT^+ EPCAM^+ CK^+ CD45^+ CTCs. Primary endpoints were CTC counts and its correlation with first line therapy. Results: Totally 180 patients were enrolled. In 174 case total CTC and CKIT CTC positive (cutoff >1) rates were 38.5% (67/177) vs 16.4% (24/148), 21.8% (31/142) vs 6.3% (9/142), 13.7% (13/95) vs 6.4% (6/94) and 40.4% (38/94) vs 15.0% (13/93) at time-points of baseline, after first-cycle-chemo, after four-cycles-chemo and disease progression. At time immediately after first-cycle-chemo, patients in CTC=0 group got statistically higher ORR (29.0% VS 7.1%, P=0.017) and DCR (9/142), 13.7% (13/95) vs 6.4% (6/94) and 40.4% (38/94) vs 15.0% (13/93) at time-points of baseline, after first-cycle-chemo, after four-cycles-chemo and disease progression. At time immediately after first-cycle-chemo, patients in CTC=0 group got statistically higher ORR (29.0% VS 7.1%, P=0.017) and DCR (9/142), 13.7% (13/95) vs 6.4% (6/94) and 40.4% (38/94) vs 15.0% (13/93) at time-points of baseline, after first-cycle-chemo, after four-cycles-chemo and disease progression. At time immediately after first-cycle-chemo, patients in CTC=0 group got statistically higher DCR (88.3% VS 58.3%, P=0.026) than in CTC=1 group. At time either after first-cycle-chemo or after four-cycles-chemo, patients in CTC=1 group got worse PFS (5.7m VS 4.0m, P=0.025) and worse DCRs (44.4% vs 62.1%, P=0.018) and PFS (5.2m vs 5.6m vs 3.1m, P=0.037). Conclusion: Monitoring EGFR mutations in plasma is a feasible and less invasive method in routine clinical practice and could be used as a predictive marker of progression on treatment with EGFR TKIs. Keywords: plasma EGFR mutations, NSCLC

MA08.09 MONITORING PLASMA EGFR MUTATIONS DURING FIRST LINE TREATMENT WITH EGFR TKIS IN NSCLC PATIENTS
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Background: Genotyping cell free circulating DNA (cfDNA) is a non-invasive method of detecting EGFR mutations (EGFRm) in plasma and may provide an option to identify patients who progress while treated with EGFR TKIs. The aim of our study was to monitor plasma EGFRm and identify dynamic case specific changes in plasma EGFRm during routine treatment of advanced EGFRm NSCLC patients. Methods: Plasma was collected from patients with advanced EGFRm NSCLC treated with first- or second-generation EGFR TKIs. Plasma EGFRm were dynamically monitored consecutively at every scheduled visit. Cobas EGFR Mutation Test v1 and v2 (Roche, USA) was used to detect 42 mutations in EGFR gene in exons 18 to 21. Liquid biopsy progression (LBP) was determined as reappearance of EGFRm in plasma after negativity during treatment or increase of EGFRm levels expressed by semi-quantitative index (SQI). Radiologic progression was determined in accordance with RECIST 1.1 criteria. Results: From May 2014, 23 patients were treated with EGFR TKIs for advanced EGFRm NSCLC, 20/23 had detectable activating mutations in plasma before any treatment and were therefore included in our analysis. Dynamic changes of plasma EGFRm during 1st line EGFR TKI treatment are shown in Figure 1. Eight patients (40%) experienced RECIST 1.1 progression while on treatment, whereas one patient was ineligible. In 4/8 patients (50%) LBP appeared at the same time as radiologic progression, in 3/8 patients (37%) LBP appeared before radiologic progression (8w, 14w, 20w before, respectively) and in 1 patient (12%) radiologic progression appeared 6w after LBP. Among patients who did not experience radiologic progression yet, some dynamic changes in cfDNA were also observed, but alterations in the SQI values were much smaller.

MA08.10 DETECTION OF THE T790M MUTATION OF EGFR IN PLASMA OF ADVANCED NSCLC PATIENTS WITH ACQUIRED RESISTANCE TO EGFR-TKI (WJ0G001TLR)
Koichi Azuma1, Takayuki Takahama2, Kazuko Sakai3, Masayuki Takeda4, Toyokazu Hida5, Masataka Hirabayashi6, Tetsuya Oguri7, Hiroshi Tanaka7, Noriyuki Ebii7, Toshiyuki Sawa7, Akihiro Bescho8, Motoko Tachihara9, Hiroaki Akamatsu10, Daisuke Himeji11, Toshiyuki Nakamatsu12, Masataka Hirose12, Noriyuki Nakajima13, Kazuhiko Nakagawa14, Kazuto Nishio15
1Division of Respiratory, Neurology, and Rheumatology, Department of Internal Medicine, Kure University School of Medicine, Kure, Japan, 2Department of Medical Oncology, Kindai University Faculty of Medicine, Osaka-Sayama, Japan, 3Department of Genome Biology, Kindai University Faculty of Medicine, Osaka-Sayama, Japan, 4Thoracic Oncology, Aichi Cancer Center Hospital, Nagoya, Japan, 5Nagoya City University Hospital, Aichi, Japan, 6Department of Internal Medicine, Niigata Cancer Center Hospital, Niigata, Japan, 7Department of Respiratory Oncology, Iizuka Hospital, Fukuoka, Japan, 8Cancer Center, Gifu Municipal Hospital, Gifu, Japan, 9Respiratory Medicine, Japanese Red Cross Okayama Hospital, Okayama, Japan, 10Division of Respiratory Medicine, Department of Internal Medicine, Kobe University Graduate School of Medicine, Kobe, Japan, 11Third Department of Internal Medicine, Wakayama Medical University, Wakayama, Japan, 12Kagawa University, Kagawa, Japan, 13Department of Internal Medicine, Miyazaki Prefectural Miyazaki Hospital, Miyazaki, Japan, 14Thoracic Surgery, Tokyo Medical University Hospital, Tokyo, Japan, 15Clinical Research Institute, National Kyushu Cancer Center, Fukuoka, Japan

Conclusion: Monitoring EGFR mutations in plasma is a feasible and less invasive method in routine clinical practice and could be used as a predictive marker of progression on treatment with EGFR TKIs. Keywords: plasma EGFR mutations, NSCLC

MA08.09 TREATMENT MONITORING IN ADVANCED NSCLC TUESDAY, DECEMBER 6, 2016 - 11:00-12:30
MA08.10 TREATMENT MONITORING IN ADVANCED NSCLC TUESDAY, DECEMBER 6, 2016 - 11:00-12:30
MA08: TREATMENT MONITORING IN ADVANCED NSCLC TUESDAY, DECEMBER 6, 2016 - 11:00-12:30

MA08.11 MONITORING THE EMERGENCE OF EGFR T790M CTDNA IN URINE FROM EGFR MUTATED NSCLC PATIENTS TO PREDICT RESPONSE TO LATER GENERATION EGFR-TKIs
Brian Woodward, Parissa Keshavarzian, Ragi Phillips, Sandeep Pingle, Vlada Melnikova, Mark Erlander, Hatim Husain
1UCSD Moores Cancer Center, La Jolla/CA/United States of America, 2Trovagene Inc, San Diego/CA/United States of America

Background: EGFR T790M mutation occurs in about half of EGFR mutated NSCLC patients with acquired EGFR-TKI resistance. It is currently unknown if switching therapy to a third generation anti-EGFR TKI based on circulating tumor DNA at first detection with urine is superior to switching therapy based on radiographic progression. Herein we demonstrate the identification of T790M in urine months before radiographic progression, the concordance for mutation detection by ddPCR in plasma compared with tumor tissue or malignant fluid specimens was 78.0% for TKI-sensitizing mutations and 65.9% for T790M. Conclusion: Noninvasive genotyping by ddPCR with cell-free DNA extracted from plasma is a promising approach to the detection of gene mutations during targeted treatment.

Keywords: T790M mutation, Acquired resistance, liquid biopsy, digital PCR

SESSION MA09: IMMUNOTHERAPY COMBINATIONS TUESDAY, DECEMBER 6, 2016 - 14:15-15:45

MA09.01 DUAL BLOCKADE OF PD-1 AND CSA/CSAR SYNERGISTICALLY PROTECTS AGAINST NON-SMALL CELL LUNG CANCER TUMOR GROWTH
Daniel Ajona, Sergio Ortiz, Haritz Moreno, Silvestre Vicent, Luis Montuenga, Francisco Locanda, Ruben Pio
Program in Solid Tumors and Biomarkers, Cima-University of Navarra, Pamplona/Spain

Background: Immunotherapy based on PD-1/PD-L1 immune checkpoint inhibitors has emerged as a powerful tool for the treatment of lung cancer. To further enhance the antitumor efficacy of individual treatments, numerous ongoing studies are trying to identify synergistic combinations that simultaneously block more than one immunomodulatory pathway. CSAR is a G protein-coupled receptor activated by CSA, an anaphylatoxin released during the activation of the complement system, a major component of innate immunity. We have previously shown in a murine model of lung cancer that pharmacological blockade of CSARi reduces cancer progression by reversing the immunosuppressive microenvironment. Thus, we hypothesized that a combined inhibition of CSAri and PD-1 may have a synergistic effect in the treatment of lung cancer.

Methods: We characterized the immunosuppressive activity of CSAri and evaluated the therapeutic efficacy of the dual administration of PD-1i and CSAri. Results: CSAri antagonists in syngeneic non-small cell lung cancer mouse models. The RPMI-14 monolayer assay was used to block PD-L1 expression on the target, which binds to complement C5s and CSa, was used to inhibit the C5s/Csar interaction. Conclusion: Our data support the notion that the efficacy of anti-PD-1 therapy is limited by the immunosuppressive tumor microenvironment. In this context, CSAri blockade combined with anti-PD1 therapy obliterates the resistance mechanisms mediated by MDSCs, improving antitumor immune responses. These findings provide a framework for the clinical evaluation of this therapeutic strategy.

Keywords: Myeloid-derived suppressor cell, PD-1, Immunotherapy, CSAri

MA09.02 PEMBROLIZUMAB + CARBOPLATIN AND PEMETREXED AS 1ST-LINE THERAPY FOR ADVANCED NON–SMALL-CELL LUNG CANCER: KEYNOTE-021 COHORT G
Corey Langer1, Shrish Gadgeel, Hossein Borghaei, Vassiliki Papadimitrakopoulou2, Amita Patel2, Steve Powell2, Renato Martins3, James Stevenson4, Shadia Jalal5, Amit Panwalkar6, James Chih-Hsin Yang7, Matthew Gabu8, Lecia Sequist9, Joseph Fiore10, Joy Ge10, Harry Rabatpulos1, Leena Gandhi1
1University of Pennsylvania, Philadelphia/PA/United States of America, 2Karmanos Cancer Institute/wayne State University, Detroit/Det/United States of America, 3Fox Chase Cancer Center, Philadelphia/PA/United States of America, 4The University of Texas MD Anderson Cancer Center, Houston/TX/United States of America, 5Southwest Cancer Accelerated Research Cooperative, San Antonio/TX/United States of America, 6Sanford Cancer Center, University of South Dakota Sanford School of Medicine, Sioux Falls/ND/United States of America, 7Emily Couic Clinical Cancer Center, University of Virginia School of Medicine, Charlottesville/VA/United States of America, 8Seattle Cancer Care Alliance, Seattle/WA/United States of America, 9University of Virginia School of Medicine, Indianapolis/IN/United States of America, 10Sanford Roger Marx Cancer Center, Fargo/ND/United States of America, 11National Taiwan University Hospital and National Taiwan University Cancer Center, Taipei/Taiwan, 12University of California, San Francisco, Helen Diller Family Comprehensive Cancer Center, San Francisco/CA/United States of America, 13Southwest Cancer Accelerated Research Cooperative, San Antonio/TX/United States of America, 14Cleveland Clinic, Cleveland/United States of America, 15Indiana University School of Medicine, Indianapolis/IN/United States of America, 16Sanford Roger Marx Cancer Center, Fargo/ND/United States of America, 17Tumor and Sex Differences, Boston/MA/United States of America, 18Merck & Co., Inc., Kenilworth/NJ/United States of America, 19Dana-Farber Cancer Institute, Boston/MA/United States of America

Background: Platinum doublet chemotherapy + bevacizumab is standard first-line therapy for patients with advanced non–small cell lung cancer (NSCLC) without genetic aberrations. Single-agent pembrolizumab exhibits...
robust antitumor activity in PD-L1–positive advanced NSCLC. Cohort G of the multicenter, open-label, phase 1/2 multicohort KEYNOTE-021 study (ClinicalTrials.gov, NCT02039674) evaluated the efficacy and safety of pembrolizumab combined with carboplatin and pemetrexed in patients with treatment-naive advanced nonsquamous NSCLC with any PD-L1 expression. Methods: Cohort G enrollment criteria included patients with stage IIIB/IV nonsquamous NSCLC, no activating EGFR mutation or ALK translocation, no prior systemic therapy, measurable disease, ECOG performance status 0-1, and adequate tumor sample for assessment of PD-L1 status, regardless of PD-L1 expression. Patients were randomized 1:1 to 4 cycles of pemetrexol 200 mg Q3W + carboplatin AUC 5 (5 mg/mL/min) + pemetrexed 500 mg/m² Q3W or carboplatin AUC 5 (5 mg/mL/min) + pemetrexed 500 mg/m² Q3W alone, followed by maintenance pemetrexed ± pembrolizumab. Pembrolizumab was given for 35 cycles. Randomization was stratified by PD-L1 expression (positive tumor proportion score, or TPS, ≥5%) vs negative (TPS <5%). Crossover to pembrolizumab monotherapy was allowed for eligible patients who experienced disease progression (RECIST v1.1) on chemotherapy. Response was assessed by central imaging vendor review every 6 weeks for first 18 weeks, every 9 weeks through year 1, and every 12 weeks in year 2. The primary end point was objective response rate (ORR); secondary end points included progression-free survival (PFS), duration of response, and overall survival (OS). Comparison between arms was assessed using the stratified Miettinen and Nurminen method (ORR) and stratified log-rank test (PFS, OS). Results: As of February 2016, 137 patients (60 in the pemetrexol + chemotherapy arm, 63 in the chemotherapy arm) had been enrolled in cohort G. Data on ORR, duration of response, safety, and preliminary PFS and OS results will be available by August 2016. Conclusion: The conclusion will be updated at the late-breaking submission stage.

Keywords: pembrolizumab, nonsmall cell lung cancer, platinum doublet chemotherapy

MA09: IMMUNOTHERAPY COMBINATIONS TUESDAY, DECEMBER 6, 2016 - 14:15-15:45

MA09.03 CISPLATIN/PEMETREXED + DURVALUMAB +/- TREMELIMUBAM IN PTS WITH ADVANCED NON-SQUAMOUS NSCLC: A CCGT PHASE IB STUDY - IND. 226 Rosalyn Juergens1, Desiree Hao1, Scott Laurie2, Mihaela Mates3, Mustapha Tehfe4, Penelope Bradbury5, Christian Kollmannsberger6, Peter Ellis1, John Hilton7, Pamela Brown-Walker6, Leslie Seymour8

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Background: Immune checkpoint inhibitors are now established therapies in many advanced cancers. Preliminary studies suggest combining immune checkpoint inhibitors with platinum-based chemotherapy may enhance anti-tumour activity. The primary objective of this multi-centre study was to evaluate the safety and tolerability of durvalumab (Du), a PD-L1 inhibitor, ± tremelimumab (Tr), a CTLA-4 inhibitor, in combination with one of four standard platinum-doublet regimens (pemetrexed, gemcitabine, etoposide (each with cisplatin) or nab-paclitaxel (with carboplatin)), in order to establish a recommended phase II dose (RP2D) for each combination. This abstract focuses on the pem/ cisplatin cohort in non-squamous non-small cell lung cancer (NSCLC). Methods: Patients (pts) with advanced NSCLC (prior treatment ≤1, advanced disease assessment ≤1), treatment with cisplatin and pemetrexed were enrolled into one of four dose levels, regardless of tumour PD-L1 status. Concurrent with chemotherapy, dose level (DL) 0 added Du 15 mg/kg IV q3w; DL1 added Du 15mg/kg q3w + Tr mg/kg q3w; DL2 added Du 15mg/kg q3w + 1 mg/kg q4wk x multiple doses; DL2b added Du 15mg/kg q3w + 1 mg/kg q4wk + 3 mg/kg q6wk (same cycle dose with maintenance pem). Pemetrexed and Du maintenance continued after completion of 4-6 cycles of pemetrexed and cisplatin. Results: Twenty-four pts (median age 61 (range 37-78); 30% female, 95% <25Q50 PFS), were enrolled (5 pts each to DL 0 and 1, 7 pts to DL 2a and 2b). Thus far 121 cycles have been administered. The majority of drug-related adverse events (AEs) were grade 2. Most AEs were related to chemotherapy; other AEs were chemotherapy or immune-related (renal, hepatic, skin and pulmonary toxicity). AEs that were considered related to Du or Tr were mainly grade 2, the most common AEs being nausea/vomiting (17%), fatigue (17%), anemia (21%) and diarrhea (13%). Two pts (DL2a) had serious related AEs (febrile neutropenia related to chemotherapy and lung infection/pneumonitis related to both chemotherapy and Du + Tr (considered a DLT)). Seventeen of the 24 patients are currently evaluable for response. The provisional objective response rate is 52.9% (95% CI: 28 -77%). Conclusion: In this PD-1 unselected patient population, Du 15mg/kg q3w and Tr 1mg/kg (multiple doses q6w) or 3mg/kg (3 doses q6w) can be safely combined with full doses of platinum-doublet chemotherapy. Additional studies with this combination are being planned.

Keywords: Immunotherapy, tremelimumab, chemotherapy, durvalumab

MA09.05 NIVOLUBAM ALONE OR WITH IPILIMUMAB IN RECURRENT SMALL CELL LUNG CANCER (SCLC): 2-YEAR SURVIVAL AND UPDATED ANALYSES FROM THE CHECKMATE 032 TRIAL Matthew Hellmann1, Scott Antonia2, Santiago Ponce1, Patrick Ott1, Emiliano Calvo1, Matthew Taylor1, Neal Ready1, Christine Hann1, Filippo De Braud3, Joseph Paul Eder4, Dirk Jäger1, Paolo Asciento, Leora Horn1, Asim Amin1, Jeff Evans5, Victor Moreno1, Atin Atmaca6, Rathi Pillai7, Jaihose Bhoile8, Petri Bono8, Noemi Reguart9, Jeffrey Schneider10, Peter Brossart11, Jennifer Diamond1, Padmanabha Sharma11, Ulrik Lassen12, Chen-Sheng Lin13, Sheng-Lin Lin13, Christian Kollmannsberger14, Scott Laurie15, Filippo De Braud16, Mustapha Tehfe17, Christian Kollmannsberger18, Scott Laurie2, Mihaela Mates3

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Background: Patients with SCLC and disease progression during/after first-line platinum-based chemotherapy have limited treatment options. Nivolumab alone and in combination with ipilimumab has shown survival benefit and durable responses in multiple tumor types. Here we present updated results for the SCLC cohort of the phase 1/2 CheckMate 032 trial (NCT01928394), which was designed to evaluate nivolumab or nivolumab/ipilimumab in a solid tumor population. Methods: Patients with advanced SCLC that progressed following 1 platinum-based chemotherapy regimen were assigned to receive nivolumab monotherapy (nivolumab-3 Q2W) or nivolumab/ipilimumab combination therapy (nivolumab-1/ipilimumab-3 Q2W). Patients were eligible regardless of platinum sensitivity or tumor programmed death ligand 1 (PD-L1) expression. The primary endpoint was ORR. Additional endpoints were duration of response (DOR), OS, PFS, and correlation of tumor PD-L1 expression with activity. Results: 214 patients have been enrolled to date (nivolumab-3, n=98; nivolumab-1/ipilimumab-3, n=116; nivolumab-3 Q2W), including for both arms treated with 1 or >2 prior regimens, respectively. Efficacy and safety data are shown (table). In the nivolumab-1/ipilimumab-3 cohort, ORR was 23% and 1-year OS was 43%. The proportion of patients with PD-L1–expressing tumors was substantially lower in previously treated SCLC in this study than that previously observed with pretreated NSCLC (10% vs 53–54% with 23% PD-L1 expression). In SCLC, responses were observed regardless of PD-L1 expression. ORR and median OS were similar in patients treated with 1 or >2 prior regimens. Rate of discontinuation due to treatment-related AEs ranged from 5% to 11%; there were 3 treatment-related deaths.

(See Table next page)
Conclusion: Durable objective responses were observed with nivolumab and nivolumab/ipilimumab in patients with previously treated SCLC, and safety profiles were consistent with other tumor types. Updated efficacy (including 2-year OS and DOR), safety, and additional subgroup analyses will be presented from the August 2016 DBL.

Keywords: Nivolumab, Ipilimumab, SCLC, PD-L1

MA09.06 VIAGENPUMATUCEL-L BOLSTERS RESPONSE TO NIVOLUMAB THERAPY IN ADVANCED LUNG ADENOCARCINOMA: PRELIMINARY DATA FROM THE DURGA TRIAL

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Background: Viagenpumatucel-L (HS-110) is an allogeneic whole-cell vaccine, selected for high expression of adenocarcinoma tumor antigens, transfected to secrete gp96-Ig. Prior studies with HS-110 (and related gp96-Ig vaccines) have shown a correlation between increases in CD8+ tumor infiltrating lymphocytes (TIL) and tumor response. The DURGA trial was designed to evaluate the combination of HS-110 and nivolumab, in an attempt to increase tumor inflammation and improve the response rates observed with nivolumab alone. Clinical Trial identifier: NCT02439450

Methods: Patients with advanced lung adenocarcinoma who received at least one prior line of therapy were assigned to two cohorts based on baseline levels of TIL in patient biopsies: low TIL (<10% CD8+ T cells) or high TIL (>10% CD8+ T cells). All patients received standard of care nivolumab 3 mg/kg every 2 weeks and weekly HS-110 for 18 weeks until intolerable adverse events, disease progression, or death. Each 9-patient Phase 1b cohort could be expanded to 30 patients in Phase 2 based on exhibited efficacy. The primary endpoint was safety and tolerability. Biopsies at baseline and Week 10 were used to track changes in TIL and PD-L1 staining. Peripheral blood mononuclear cells (PBMC) were evaluated by flow cytometry for detection of circulating leukocyte subsets. ELISPOT was used to track antigen-specific immune response.

Results: HS-110 vaccine and nivolumab combination was well tolerated with a safety profile consistent with single-agent nivolumab. Among the 34 enrolled patients, only 4 had optional biopsies which showed 2 patients with high and 2 with low TILs. PD-L1 was >5% in 3 patients. IFN-γ ELISPOT assay defined 4 patients as immune responders (doubling of IFN-γ-secreting cells after re-stimulation with total vaccine antigen and individual cancer antigens, IR) and 4 patients as non-immune responders (NIR). The overall response rate (ORR) was 50% in the IR patients and 0% in the NIR patients. At the time of the data cutoff, 6 patients remain alive, including the 4 IR patients, with ongoing responses for 150 to 326 days. Patients with objective response also exhibited injection site reactions and maculopapular rash consistent with HS-110 mechanism of action, decreased Myeloid Derived Suppressor Cells (MDSC) in the blood, and increased markers of activated CD8+ T cell subsets by flow cytometry (CD8+CD38+CD16+). Although the pathology specimens were sub-optimal in the two responding patients, the limited tissue available showed lower baseline TILs in both patients. Conclusion: Allogeneic gp96-based vaccination may have synergistic activity in combination with immune checkpoint inhibitors.

Keywords: Immunotherapy, Checkpoint Inhibitor, Nivolumab, Vaccine

MA09.07 PHASE I TRIAL OF IN SITU VACCINATION WITH CCL21 GENE-MODIFIED DC INDUCES SPECIFIC SYSTEMIC IMMUNE RESPONSE AND TUMOR INFILTRATING CD8+ T CELLS


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Background: Intratumoral (IT) infiltration by activated immune effector cells is associated with a significantly better prognosis, however, tumor-associated immune suppression commonly occurs in non-small cell lung cancer (NSCLC). CD8+ T cell and dendritic cell (DC) infiltration is an independent favorable prognostic indicator. CCL21 is a lymphoid chemokine that chemotacts both lymphocytes and DC. Our aim was to investigate anti-tumor specific systemic immune responses and tumor infiltrating CD8+ T cells (CD8+ TIL) in NSCLC patients in response to in situ vaccination via IT administration of autologous DC transduced with a replication-deficient adenoviral (Ad) vector expressing the secondary lymphoid chemokine (SLC/CCL21) gene. Here, we conducted a phase I trial and evaluated safety and immune responses following in situ vaccination. Methods: Sixteen stage IIIb/IV NSCLC subjects received two vaccinations (1 x 10^7, 5 x 10^7, 1 x 10^8, or 3 x 10^8 dendritic cells/injection) by CT- or bronchoscopy-guided IT injection (days 0 and 7). Immune responses were assessed by tumor antigen-specific peripheral blood lymphocyte induction of IFN-γ, ELISPOT and the secondary lymphoid chemokine (SLC/CCL21) gene. Results: Twenty-five percent (4/16) of patients had stable disease at day 56 follow-up by RECIST criteria. Median survival was 3.9 months. Four possible vaccine-related grade 1 adverse events (AE) occurred in 3 patients with no clear association to dose or schedule; the AE included flu-like symptoms, blood-tinted sputum after each injection, nausea, and fatigue. ELISPOT assays revealed 38% (6/16) of patients had systemic responses against tumor associated antigens (TAA). Durable CD8+ T cell infiltration was induced in 54% of subjects (7/13; 3.4 fold average increase in the number of CD8+ T cells per mm³). Patients with increased intratumoral CD8+ T cells following vaccination showed significantly increased PD-L1 mRNA expression (p=0.02). Conclusion: Intratumoral vaccination with Ad-CCL21-DC was well-tolerated and resulted in 1) induction of systemic tumor antigen-specific immune responses and 2) enhanced tumor CD8+ T cell infiltration. DC-CCL21 in situ vaccination may be a promising approach to induce tumor CD8+ T cell infiltration in combination with checkpoint inhibitor therapy.

Keywords: Lung cancer, PD-L1, CCL21, dendritic cells

MA09. IMMUNOTHERAPY COMBINATIONS

TUESDAY, DECEMBER 6, 2016 - 14:15-15:45

MA09.08 FIRST-IN-HUMAN PHASE I STUDY OF ABVV-399, AN ANTIBODY-DRUG CONJUGATE (ADC) TARGETING C-MET, IN PATIENTS WITH NON-SMALL CELL LUNG CANCER (NSCLC)

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Background: The c-Met receptor is overexpressed in ~50% of patients with NSCLC. ABVV-399 is a first-in-class ADC composed of ABT-700, an anti-c-Met...
antibody, conjugated to monomethyl auristatin E (a microtubule inhibitor). Preclinical data support ABBV-399 as a unique strategy to deliver a potent cytotoxic directly to c-Met+ tumor cells. Methods: In a 3+3 dose-escalation design, ABBV-399 was administered at doses ranging from 0.15 to 3.3 mg/kg once every 21 days to patients with advanced metastatic solid tumors (NCT02099058). ABBV-399 was then studied in a dose-expansion cohort in 16 patients with advanced c-Met+ (immunohistochemistry (IHC) H-score ≥150) NSCLC that had progressed on ≥2 prior lines of therapy. ABBV-399 was also studied in combination with erlotinib in 10 patients with NSCLC, 8 of whom were c-Met+. Overexpression of c-Met was assessed by an IHC assay utilizing the SP44 antibody (Vantona; Tuscon, AZ, USA). Results: As of June 27, 2016, 48 patients with solid tumors received ≥1 dose of ABBV-399. The dose-limiting toxicity (DLT) for ABBV-399 was febrile neutropenia, which occurred in 2 patients (1 each at 3 and 3.3 mg/kg). There were no treatment-related deaths. Monotherapy treatment-related adverse events (AEs) occurring in ≥10% of patients (including all dose levels and all grades) were fatigue (25.0%), nausea (22.9%), neuropathy (16.4%), decreased appetite (12.5%), vomiting (12.5%), and hypoalbuminemia (10.4%). Based primarily on safety and tolerability, a 2.7 mg/kg dose was chosen for dose expansion in patients with c-Met+ advanced NSCLC. Three of 16 (19%) ABBV-399-treated c-Met+ NSCLC patients had a confirmed partial response (PR) with duration of response (DOR) ≥3, ≥3, and ≥3.5 months. At week 12, 6 of 16 patients treated (37.5%) had disease control. Ten patients received ABBV-399 in combination with erlotinib. No DLTs were observed and AEs related to ABBV-399 occurring in ≥2 patients were acneiform rash (40.0%), fatigue (30.0%), and dry skin (20.0%). Three of 8 (37.5%) evaluable ABBV-399 + erlotinib-treated c-Met+ patients had a confirmed PR with DOR ≥2, ≥4, and ≥5 months. Two of the 3 patients with PR had EGFR-mutated tumor, and previous TKI- and platinum-based chemotherapy had failed. Conclusion: ABBV-399 is well tolerated at a dose of 2.7 mg/kg every 21 days and has demonstrated antitumor activity in patients with c-Met+ NSCLC both as monotherapy and in combination with erlotinib. Updated data of antitumor activity and safety of ABBV-399 as monotherapy and in combination with erlotinib in c-Met+ NSCLC patients will be presented. Keywords: antibody drug conjugate, non-small cell lung cancer (NSCLC), c-Met, Erlotinib

MA09: IMMUNOTHERAPY COMBINATIONS TUESDAY, DECEMBER 6, 2016: 14:15-15:45

MA09.10 A NAPI2B ANTIBODY-DRUG CONJUGATE INDUCES DURABLE COMPLETE TUMOR REGRESSIONS IN PATIENT-DERIVED Xenograft Models of NSCLC

Donald Bergstrom, Natalya Bodky, Alex Yurkovetsky, Laura Poling, Mao Yin, Marina Protopopova, Mike Devit, Liuliang Qin, Dmitry Gumerov, Helena Ter-Ovanesyan, Rebecca Mosher, Timothy Lowinger

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Background: The sodium-phosphate transporter NaPi2b is expressed at high levels in a majority of non-squamous non-small cell lung cancers (NSCLC), suggesting it may be an attractive therapeutic target for antibody-drug conjugate (ADC) development in this disease. However, NaPi2b is also expressed at high levels in type II alveolar cells, raising the potential for normal tissue toxicity with this approach. XMT-1536 is an ADC comprised of a humanized antibody against NaPi2b and approximately 15 auristatin-derived payload molecules per antibody conjugated via a multivalent hydrophilic polymer (Fleximer). The auristatin payload is enzymatically cleaved upon ADC cytotoxin directly to c-Met+ tumor cells.

Methods: The anti-tumor activity of XMT-1536 was evaluated in seven patient-derived xenograft models of NSCLC adenocarcinoma, chosen for high NaPi2b expression and representing a spectrum of oncogenic driver mutations prevalent in NSCLC adenocarcinoma (including tumors without oncogenic drivers). The standard dose of XMT-1536 used across models was 3 mg/kg administered intravenously once weekly for 3 weeks (last dose on Day 14). Experiments were conducted in NSCLC models under a pre-specified endpoint or Day 60. XMT-1536 was also evaluated for tolerability in a cynomolgus monkey study.

Results: At the 3 mg/kg dose, XMT-1536 was active in 6/7 models: complete tumor regression in 3 models, partial tumor regression in 1 model, and significant tumor growth inhibition in 2 models. In 3 of the 4 models where XMT-1536 induced tumor regression, regressions were durable, with a majority of the animals maintaining partial or complete regression at Day 60. The antibody component of XMT-1536 is cross-reactive with cynomolgus NaPi2b with similar affinity as human NaPi2b. XMT-1536 was well tolerated up to 5 mg/kg (≤29% mg/m² auristatin payload equivalents), the highest dose tested. There was no body weight loss, no clinical observations attributable to XMT-1536, and no evidence of neuropenia. On pathology, there was minimal mixed inflammatory cell infiltrate in the lung in 1 high dose animal at each necropsy time point, but no evidence of significant lung toxicity. Exposure to XMT-1536 indicated good conjugate stability, low exposure to free drug payload in plasma (<1 ng/mL), and supported the 3 mg/kg dose level in mouse studies as a potentially clinically-relevant dose. Conclusion: These results indicate XMT-1536 can achieve durable tumor regressions in murine patient-derived NSCLC adenocarcinoma models at doses associated with good tolerability in a non-human primate model, and support evaluation of XMT-1536 in patients with NSCLC.

Keywords: Novel Therapies, Antibody-drug conjugate, Adenocarcinoma, Targeted chemotherapy

MA09: IMMUNOTHERAPY COMBINATIONS TUESDAY, DECEMBER 6, 2016: 14:15-15:45

MA09.11 EFFICACY AND SAFETY OF NECITUMUMAB AND PEMBROLIZUMAB COMBINATION THERAPY IN STAGE IV NONSQUAMOUS NON-SMALL CELL LUNG CANCER (NSCLC)

Benjamin Besse 1, Pilar Garriado 2, Javier Puente 3, Alexis Cortot 4, Maria Eugenia Olmedo 5, Maurice Pérol 6, Maciej Gijl 7, Grace Chao 8, Javad Shahidi 9, Jaafar Bennoune 10

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Background: Trials of anti-EGFR necitumumab and anti-PD-1 pembrolizumab demonstrate the anti-tumor activity of each agent in NSCLC. Methods: Single-arm, multicenter Phase Ib study to investigate effectiveness and safety of necitumumab combined with pembrolizumab in patients with Stage IV NSCLC (NCT02451930). In Part A, escalating doses of necitumumab (600 mg and 800 mg IV) were administered on Day 1 and Day 8 every 3 weeks (Q3W) in combination with pembrolizumab (200 mg IV) on Day 1 Q3W. In the absence of dose limiting toxicity, Part B (expansion cohort) was planned with necitumumab 800 mg in 27 squamous and 27 nonsquamous NSCLC patients. Major eligibility criteria included: progression after ≥1 platinum-based chemotherapy, and ECOG PS 0-1. Study objectives were to evaluate tolerability and ORR by RECIST 1.1. PD-L1 status was centrally assessed using PD-L1 IHC 22C3 pharmDx assay (considered negative, weak positive, strong positive if ≥1%). 10% of tumors were stained, respectively. Results: The interim analysis population includes 34 nonsquamous patients (median age 61 years, 68% men, 21% never smokers, PD-L1 status: negative, 50% [17/34], positive weak/strong, 15% [5/34]/15% [5/34]; unknown 21% [7/34]). Median follow-up was 6.0 months. Ten patients (29.4%) had PR (confirmed and unconfirmed) (PRs by PD-L1 status: negative, 18% [3/17]; positive weak/strong, 60% [3/5]/60% [2/5]; unknown status, 2 patients). DCR was 67.6%, PFS rate at 6 months was 55.1% (95% CI, 36.2-70.6); median PFS was 6.9 months (95% CI, 2.7-NR). Most common Grade ≥3 AEs were skin rash (14%), nausea (12%), increased lipase (9%); 1 patient died due to an AE (respiratory tract infection). Five patients (14.7%) discontinued therapy because of an AE.

Figure: Change in Target Tumor Burden from Baseline (RECIST 1.1)

Conclusion: Safety profile corresponds to individual profiles for both drugs, with no additive toxicities. These preliminary data suggest activity of this combination in a pretreated nonsquamous NSCLC population, irrespective of PD-L1 status.

Keywords: non-small cell lung cancer, Necitumumab, pembrolizumab

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SESSION MA10: FACING THE REAL WORLD: NEW STAGING SYSTEM AND RESPONSE EVALUATION IN IMMUNOTHERAPY
TUESDAY, DECEMBER 6, 2016 - 14:15-15:45

MA10.01 VALIDATIONS OF THE 8th AJCC/UICC LUNG CANCER STAGING SYSTEM IN A LARGE NORTH AMERICA COHORT
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Background: The new 8th AJCC/UICC lung cancer staging system was developed and validated using the International Association for the Study of Lung Cancer (IASLC) database, which contains 84,708 lung cancer patients worldwide, but only 5% of patients in this database came from North America. The goal of this study is to validate the prognostic performance of this new staging system, focusing on the upgraded “T” and “M” parameters, in North American lung cancer patients. Methods: We analyzed 1,163,465 non-small cell lung cancer (NSCLC) cases collected from 2004 to 2013 in the United States in the National Cancer Database (NCDB). After excluding patients with more than one malignant primary tumor or tumor size larger than 10 cm, 545,776 NSCLC patients were included in the final data analysis. We defined 8th T and M parameters according to the primary coding guidelines of the Collaborative Staging Manual and Coding Instructions for the new 8th AJCC/UICC lung cancer staging system. Kaplan-Meier survival curves and log-rank tests were used to compare survival difference among different stage groups, and Cox regression models were used for multivariate analysis adjusting for potential confounders. Results: We validated that the new staging system can provide better survival prediction for NSCLC patients in the NCDB cohort than the existing 7th staging system. The median survival time for T1a is 58 months (N=15,860), for T1b is 47 months (N=78,379), and for T1c is 25 months (N=79,828) (p < 0.001). The median survival time for T2a is 19 months (N=111,925), for T2b is 12 months (N=54,601), for T3 is 10 months (N=105,234), and for T4 is 7 months (N=99,840) (p < 0.001). And the median survival time for M0 is 25 months (N=411,048), for M1a is 8 months (N=49,352), for M1b is 6 months (N=42,224), and for M1c is 3 months (N=15,926 cases) (p < 0.001). Multivariable analysis showed that these staging parameters are significantly associated with survival when adjusting other factors. Conclusion: Both upgraded “T” and “M” parameters of the 8th AJCC/UICC lung cancer staging systems are significantly associated with NSCLC patient survival outcomes using data from the NCDB, indicating a good validation performance in patients from North America.

Keywords: AJCC/UICC cancer stage, non small cell lung cancer, national cancer database, survival analysis

MA10.02 CLINICAL STAGING IN THE 8TH EDITION TNM FOR LUNG CANCER IS INACCURATE
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Background: The new classification for lung cancer refines the T-descriptor criteria into more categories. We examined whether this affects the accuracy of clinical staging, and how this affects the final stage of patients. Methods: 71 patients underwent resection for primary lung cancer from January 2014 to December 2014. T-component was measured based on the maximum tumour size on CT, PET-CT and histology report. The possible effect on staging based size on CT, PET-CT and histology report. The possible effect on staging based on T-component was compared between both TNMs. Results: PET-CT more accurately estimates the pathological size of the tumor (mean difference from histology: CT 3mm (range-1.6 to 2.6cm) and PET-CT 1.3mm (2 to 2.5cm). Discordance between radiological and pathological T-stage was higher with the 8th edition CT 31(44%) and PET-CT 33(43%), 8th edition CT 31(44%) and PET-CT 29(41%) (CT p=0.01, PET-CT p=0.71). The final stage groupings were also more discrepant in the 8th edition. Concordance was for CT 7th Edition 37(54%) vs 8th Edition 21(31%) (p=0.001), and for PET-CT 34(41%) vs 19(28%) (p=0.001). The discrepancy in stage grouping is contributed significantly by T-stage discordance. In the 30 patients who were not upstaged pathologically by pleural invasion or nodal staging, there is a 50% increase in inaccurancy of clinical staging in the 8th edition. The CT concordance was 7th edition 24(80%), 8th edition 13(63%) (p=0.001), and for PET-CT 23(77%) vs 10(33%) (p=0.001). Conclusion: We showed that the 8th edition TNM lung cancer staging system was associated with a significant increase in discordance between clinical and pathological staging due to differences in measurement of tumour size and consequently T-stage groupings by different modalities. This has implications for prognostication and clinical trial interpretation especially in patients who do not undergo surgery for pathological stage confirmation.

Keywords: Staging, 7th Edition, lung cancer, 8th Edition

MA10.03 INVESTIGATING THE POTENTIAL UTILITY OF THE ALTERNATIVE 9TH EDITION IASLC NODAL STAGING CLASSIFICATION IN NSCLC
Timothy Edwards, Haval Balata, Charlene Tennyson, Philip Foden, Anshuman Chaturvedi, Philip Crosbie, Richard Booton, Matthew Evison
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Background: The IASLC lung cancer staging project recently published recommendations for the 8th edition of the TNM classification of lung cancer. This recommends the same N descriptors be used, however, further analysis of an alternative system (proposed 9th Edition) was recommended. The aim of this retrospective study was to assess the utility of this proposed nodal staging system at a large UK tertiary lung cancer centre. Methods: Patients who underwent surgical resection for non-small cell lung cancer between 2011-2014 (allowing minimum of 2 years follow-up) were identified from a prospective database (n=1308). Stratification of pathological N-stage as per
the iASCLL proposal was performed: N0, single station N1 (N1a), multi-statin N1 (N1b), single station N2 without N1 involvement – skip metastases – (N2a), single station N2 with N1 involvement (N2a2), multi-station N2 (N2b) and N2. Survival data was obtained from national death registries. Results: There is a significant effect of N-stage on mortality using Cox proportional hazards regression analysis, using pN0 (n=848) as the reference group and adjusting for sex, age and histology (table 1). There appears to be similar survival outcomes between multi-station N1 (pN1b) and single station N2 skip metastases (pN2a2), and single station N2 with N1 involvement (pN2a23) and multi-station N2 (pN2b).

Table 1.

<table>
<thead>
<tr>
<th>N-stage</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>pN1a (n=166)</td>
<td>1.68</td>
<td>(1.26, 2.26)</td>
<td>0.001</td>
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<tr>
<td>pN1b (n=55)</td>
<td>2.25</td>
<td>(1.49, 3.39)</td>
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<td>pN2a2 (n=50)</td>
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<td>(1.46, 3.45)</td>
<td>&lt;0.001</td>
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<tr>
<td>pN2a2 (n=81)</td>
<td>2.47</td>
<td>(1.25, 4.03)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>pN2b (n=67)</td>
<td>2.99</td>
<td>(2.09, 4.27)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Conclusion: The presented 8th edition N-staging classifications appear to add additional insight into prognosis. However, interpretation is limited by the small numbers of patients within the pN1/pN2 sub-groups. 65% of this large cohort were pN0 and acted as the reference group and a further 5% were pNx as no nodes were submitted. Furthermore, the accuracy of pN-staging is reliant on the quality of intra-operative lymph node sampling. Although significant improvements have been made in this timeframe at our centre (published previously), any sub-optimal performance has the potential to affect the validity of the results, particularly if multi-station N2 disease is missed.

Keywords: Surgical staging, TNM classification, non small cell lung cancer

M1A0.05 PROPOSALS FOR THE NOVEL CLINICAL T CATEGORIES BASED ON THE PRESENCE OF GROUND GLASSOPACITY COMPONENT IN LUNG ADENOCARCINOMA

Aritoshi Hattori, Takeshi Matsunaga, Kazuya Takamochi, Shikai Oh, Kenji Suzuki
General Thoracic Surgery, Juntendo University, Tokyo/Japan

Background: In lung adenocarcinomas, the histologic lepidic growth pattern tends to correlate with the ground glass opacity (GGO) component, while solid components correspond with invasive adenocarcinoma. The eighth edition of the TNM staging system suggests that the tumor size be determined according to the invasive size excluding the lepidic component. However, this new concept causes fatal confusion, i.e., tumors are classified into a same T category despite the part-solid or pure-solid appearances provided they showed a same solid component size. Methods: Between 2008 and 2012, we retrospectively evaluated 719 surgically resected chest lung adenocarcinomas that measures 30mm or less in total dimension to assess the prognostic impact of the presence of GGO among the eighth TNM classification. According to the new T category, it was defined based on the solid component size as follow: Tis: 0 cm (pure-GGO), T1mi: ≤5 mm, T1a: 6-10 mm, T1b: 11-20 mm, T1c: 21-30 mm. Furthermore, all tumors were classified into 2 groups, i.e., GGO or Solid arms based on the presence of GGO component. Results: Of the cases, 133 (18%) were categorized in Tis, 88 (12%) in T1mi, 121 (16%) in T1a, 244 (34%) in T1b and 133 (18%) in T1c, respectively. Multivariate analysis revealed that both a presence of GGO and solid component were independent significant prognostic factors (p=0.007, 0.002). The 5y-overall survival (OS) was 99.2% in Tis, 95.8% in T1mi, 96.5% in T1a, 81.8% in T1b and 66.4% in T1c (p=0.038) with a median follow-up period of 56 months. When we evaluated the impact of T category based on GGO presence, the 5y-OS was significantly different between GGO and Solid arm in each T categories (Tis: 99.0% vs. 95.1%, p=0.045, T1mi: 99.0% vs. 73.3%, p=0.004, T1a: 90.0% vs. 62.6%, p=0.046). Furthermore, clinical T categories significantly separated the OS in Solid arm (p=0.015) (T1a vs. T1b; p=0.090, T1b vs. T1c; p=0.037). In contrast, the 5y-OS was approximately 90% or more in GGO arm despite their T categories. Moreover, according to radiological and pathological correlations, the rates of AIS was only 5.6% in Tis, and 5% showed invasive adenocarcinoma even in T1mi. Conclusion: Clinical T category should be considered based on the presence of GGO on thin-section CT, and tumor size should be applied exclusively to radiological solid lung cancer. In contrast, oncological outcomes of the tumor with GGO component were excellent despite their T categories, which should be described as Tis for pure-GGO, and T1a for part-solid tumor.

Keywords: lung cancer, GGO component, TNM staging

M1A0.10 FACING THE REAL WORLD: NEW STAGING SYSTEM AND RESPONSE EVALUATION IN IMMUNOTHERAPY

Tuesday, December 6, 2016 - 14:15-15:45
MA10.10 [18F]-FDG-PET/CT EARLY RESPONSE TO NIVOLUMAB IN NSCLC

Dimitri Bellevere1, Gregory Petyt1, Giulia Collette1, Claude Hossein-Foucher1, Simon Baldacci1, Anne Baranzelli1, Franck Semali2, Alexis Cortot1

1Nuclear Medicine Department, Lille University Hospital, Lille/France, 2Thoracic Oncology, Lille University Hospital, Lille/France

Background: Nivolumab is approved for treatment of squamous and non-squamous advanced NSCLC. Since nivolumab restores antitumor immunity, it is not clear whether 18F-FDG-PET/CT is able to distinguish response from tumor progression. We evaluated early metabolic patterns of response to nivolumab in advanced NSCLC patients. Methods: We retrospectively reviewed PET/CT scans and paired CT scans from 22 patients with advanced NSCLC who received nivolumab 3mg/kg every 2 weeks and performed PET/CT before and after 4 infusions of nivolumab. Total Lesion Glycolysis (TLG) and Metabolic Tumor Volume (MTV) of every lesion up to 5 per patient were measured on baseline and follow-up PET/CT. Percentage changes in MTV (ΔMTV) and TLG (ΔTLG) between the two PET/CT were calculated. Patients were classified into responders (nivolumab for 6 months), non-responders (nivolumab ≤6 months) or having pseudo-progression (PP, nivolumab and CT evaluation criteria). Results: Among 22 patients, 6 (27%) were responders, 15 (68%) were non-responders and 1 (4.5%) had PD. Baseline MTV and TLG were significantly lower in responders than in non-responders (medians 27 vs. 63 mL, p=0.03 and 124 vs. 254 g, p=0.04, respectively). After 4 infusions of nivolumab, metabolic parameters were significantly lower in responders than in non-responders (median ΔMTV 35 g, 9% in responders and +236% and +312% in non-responders, which was significantly different (p=0.0005). The only patient with PD had lower ΔMTV (+11%) and ΔTLG (+4%) than non-responders patients. Conclusion: In NSCLC, objective response and disease progression upon nivolumab usually translate into early and clear-cut patterns of change in PET/CT. Early PET/CT may help to distinguish progression from pseudo-progression.

Keywords: response evaluation, Nivolumab, PERCIST, RECIST
MA10.11 COMPARISON AMONG DIFFERENT RADIOLOGICAL CRITERIA FOR ASSESSING RESPONSE TO NIVOLUMAB IN ADVANCED NON-SMALL CELL LUNG CANCER

Francesco Grossi1, Giovanni Rossi1, Erika Rijavec, Giulia Barletta, Federica Biello, Claudia Magnioni1, Simone Mennella1, Maria Giovanna Dal Bello1, Roberta Distefano1, Giuseppe Cittadini1, Franco Merlo2, Carlo Genova1

1Lung Cancer Unit, San Martino Hospital - National Institute for Cancer Research, Genova/Italy, 2Radiology, San Martino Hospital - National Institute for Cancer Research, Genova/Italy, 3Clinical Trials Unit, San Martino Hospital - National Institute for Cancer Research, Genova/Italy

Background: Immune check-point inhibitors have dramatically changed the management of advanced non-small cell lung cancer (NSCLC); however, their mechanism of action creates concerns on the most appropriate method to determine radiological responses to this drug class. The aim of this study is to compare a set of different evaluation criteria for patients receiving nivolumab for advanced NSCLC.

Methods: Patients with pre-treated advanced NSCLC enrolled in a single-institutional translational research study in the San Martino Hospital - National Institute for Cancer Research, Genova, Italy and received nivolumab (3 mg/kg every 14 days). Computed tomography (CT) was performed at baseline and after every 4 administrations. The assessments were performed according to immune-related response criteria (irRC), response evaluation criteria in solid tumors (RECIST 1.1), World Health Organization (WHO), and immune-related RECIST (irRECIST), which are recently proposed based on the original RECIST with the following differences derived by irRC: 1) new lesions do not automatically define progressive disease (PD), but are added to the target lesions count; 2) PD has to be confirmed with a subsequent CT-scan after 2 additional cycles. The concordance among the different criteria was determined with Cohen’s kappa coefficient (K).

Results: Fifty-two patients were evaluable: median age = 70 years (44-85); male/female: 70/30%; current or former smokers= 87%; non-squamous/squamous histology= 79/21%; median number of cycles= 6 (4-29). The following responses were observed:

<table>
<thead>
<tr>
<th>Partial Response</th>
<th>Stable Disease</th>
<th>Progressive Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>RECIST 1.1</td>
<td>4 (7.7%)</td>
<td>19 (36.5%)</td>
</tr>
<tr>
<td>irRC</td>
<td>3 (5.8%)</td>
<td>23 (44.2%)</td>
</tr>
<tr>
<td>WHO</td>
<td>3 (5.8%)</td>
<td>20 (38.5%)</td>
</tr>
<tr>
<td>irRECIST</td>
<td>4 (7.6%)</td>
<td>24 (46.2%)</td>
</tr>
</tbody>
</table>

Best Response:

<table>
<thead>
<tr>
<th>Partial Response</th>
<th>Stable Disease</th>
<th>Progressive Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>RECIST 1.1</td>
<td>9 (17.3%)</td>
<td>14 (26.9%)</td>
</tr>
<tr>
<td>irRC</td>
<td>8 (15.4%)</td>
<td>19 (36.5%)</td>
</tr>
<tr>
<td>WHO</td>
<td>7 (13.5%)</td>
<td>17 (32.7%)</td>
</tr>
<tr>
<td>irRECIST</td>
<td>11 (21.2%)</td>
<td>18 (34.6%)</td>
</tr>
</tbody>
</table>

Generally, the concordance between first evaluation and best response was good for all the criteria (K ranging from 0.783 to 0.839); the concordance between irRECIST and irRC was high (K= 0.828) and RECIST 1.1 had a good concordance with irRC (K= 0.734), irRECIST (K= 0.767), and WHO (K= 0.766).

Conclusion: The different response assessment methods were generally concordant. Since response is more easily assessed with irRECIST than with irRC, the former might be proposed as an appropriate method of response evaluation.

Keywords: Response criteria, RECIST 1.1, immune-related response criteria, Nivolumab

SESSION MA11: NOVEL APPROACHES IN SCLC AND NEUROENDOCRINE TUMORS
TUESDAY, DECEMBER 6, 2016 - 14:15-15:45

MA11.01 MOLECULAR PROFILING OF LARGE CELL NEUROENDOCRINE CARCINOMA USING CAPTURE-BASED TARGETED SEQUENCING

Zhen Zhou1, Lei Zhu2, Shun Lu1, Jie Zhang2

1Department of Shanghai Lung Cancer Center, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai/China, 2Department of Pathology, Shanghai Chest Hospital, Shanghai/China

Background: Conventionally, the classification of lung cancer and many other malignancies is determined by the histology of a tumor. Large cell neuroendocrine carcinoma (LCNEC) is traditionally classified as a histological variant of large cell carcinoma (LCC), which is a subtype of non-small cell lung cancer (NSCLC). However, LCNEC exhibits differential cytological, morphological, clinical and biological features than those of classic LCC, thus rendering controversy regarding its classification. In 2015, with the integration of immunohistochemical analyses, the World Health Organization (WHO) has re-classified LCNEC under neuroendocrine tumors. Due to the rareness of LCNEC, few studies have been conducted on the molecular genetic profiling of LCNEC. In this study, we characterized molecular alterations associated with a cohort of LCNEC, SCLC and LCC using capture-based targeted sequencing.

Methods: We performed capture-based targeted sequencing on 30 surgically resected samples from patients with lung cancer using Biontime Biotech’s OncoScreen Panel. This panel, consisting of 494 exons and critical introns of 295 genes, covering multiple classes of somatic mutations, including single nucleotide variation (SNVs), rearrangements, copy number variations (CNVs) and insertions and deletions (INDELs), can be used to detect genetic alterations both qualitatively and quantitatively. Among the 30 patients, 15 of them were diagnosed with LCNEC, 5 with LCC and 10 with small cell lung cancer (SCLC).

Results: While no statistically significant difference was observed in total number of mutations among the three subtypes, LCC carries the most number of somatic mutations followed by LCNEC then SCLC. Overall, we identified 131 mutations with TP53 being the most frequently mutated gene in all three subtypes. Genes with recurrent somatic mutations detected in LCC, but not in LCC or SCLC include RUNX1, ERBB4, BRCA1, and EPHA3. Copy number analysis revealed a higher prevalence of CNV in LCNEC, with 60% of cases harboring such alteration. There is no common CNVs shared among all three subtypes. NFKBIA amplification is the only common CNV found in both LCNEC and LCC; and AKT2 amplification is shared by LCNEC and SCLC. Most CNVs are subtype-specific. Interestingly, one RET-fusion was discovered in one LCC sample and one EGFR exon 19 deletion accompanied by EGFR copy number amplification was discovered in one LCNEC sample. Conclusion: Targeted deep sequencing reveals distinct genetic profile for LCNEC compared to LCC and SCLC. LCNEC harbors more CNV and contains a panel of genes, including RUNX1, ERBB4, BRCA1 and EPHA3 that are more frequently mutated compared to LCC and SCLC.

Keywords: LCNEC, NGS, molecular profiling

MA11.02 MUTATIONAL BURDEN IN PULMONARY NEUROENDOCRINE TUMORS (PUNETS)

Ivana Suluč1, Myriam Kossai1, Gwénaël Le Teuff1, Marc Degolier1, Nicolas Dorvaut1, Letizia Giononcelli1, Vincent De Montpreville1, Bastien Job1, Maria Bluthgen1, Benjamin Besse2, Jean-Charles Soria2, Julien Adam2, Jean-Yves Scoccaze3, Eric Baudin4, David Planchard1

1Medical Oncology, Gustave Roussy, Villejuif/France, 2Gastroenterology, Gustave Roussy, Villejuif/France, 3Instituto Clinico Humanitas, Rozzano/Italy, 4Centre Chirurgical Marie-Lannelongue, Le Plessis-Robinson/France, 5Medical Oncology Department, Gustave Roussy, Villejuif/France, 6Department of Cancer Medicine, Gustave Roussy, Villejuif/France

Background: Tumor mutational load (TML) by whole-exome sequencing (WES) is a potential determinant of response to immune checkpoint blockers. The use of PD-L1 as a predictive biomarker for use of PD-1/PD-L1 inhibitors is limited. To date, there are few data concerning TML in pulNETs. Methods: WES was performed in fresh-frozen tumor-normal pairs from 35 typical carcinoid (TC), 4 atypical carcinoid (AC) and 9 large-cell neuroendocrine carcinoma (LCNEC) consecutively collected. Exome enriched libraries were sequenced on an Illumina HiSeq 2000 with a paired-end 2 x 100 bp protocol. Reads were aligned to the reference hg19 using an implementation of the Burrows-Wheeler Aligner, and a BAM file was produced for each tumor and normal sample using the Picard pipeline. The MuTect algorithm was used to identify SNVs in WES data. We used a minimal allelic fraction cutoff of 0.1. Patients’ characteristics and TML were described (median and interquartile for quantitative variables and frequencies for qualitative variables). To evaluate the effect of some factors on the TML, an analysis of variance was used. A log transformation was performed according to the distribution of the TML. The median follow-up was estimated using the Schemper’s method. The number of relapses and deaths was reported. Results: Cohort included 24 male and 24 female. Median age at diagnosis was 57 (Q1= 46; Q3=70) years, 38% of carcinoids (TC+AC) and 88% of LCNEC were smokers, 26 (54%) stage I, 16 (34%) stage II, 3 (6%) stage III and 3 (6%) stage IV. All patients underwent surgery, 11 (21.2%) received neoadjuvant treatment. Median follow-up was 32.6 months (min= 4.4; max= 179.9) months; there were 8 (17%) relapses (6/9 LCNEC, 2/39 carcinoids) and 10 deaths. On average, 11.6 Gb of sequence were produced per sample, aiming a mean coverage of 72X. Overall median TML was 0.31/Mb (Q1= 0.22, Q3= 0.40).

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Hospital, Shanghai Jiao Tong University, Shanghai/China

Keywords: Pulmonary NEUROENDOCRINE TUMORS (PUNETS), Genotype, TML
MA11.03 INSM1 IS A NOVEL BIOMARKER AND A CRUCIAL REGULATOR OF THE NEUROENDOCRINE DIFFERENTIATION PATHWAY IN NEUROENDOCRINE TUMOURS OF THE LUNG

Fujio Kosuke1, Kazuhiro Yasufuku1, Makoto Suzuki1, Takaaki Ito2
1Division of Thoracic Surgery, University Health Network, Toronto/ON/Canada,
2Department of Pathology and Medical Research, Medical School, Kumamoto University, Kumamoto/Japan

Background: Insulinoma-associated protein 1 (INSM1) is expressed predominantly in embryonic differentiating neuroendocrine (NE) tissues, and is considered a potential research tool for NE tumours.

Methods: We compared INSM1 as an immunohistochemical biomarker for NE tumours of the lung to conventional markers (chromogranin A (CGA), synaptophysin (SYP), and CD56). To elucidate the biological function of INSM1 in the NE differentiation pathway, we conducted INSM1 gene knockdown/overexpression experiments using human lung cancer cell lines.

Results: INSM1 was expressed in 100% of SCLCs (44/44), Large cell neuroendocrine carcinoma tumours (7/7), and Carcinoids (11/11), but was not expressed in NSCLCs (90 adenocarcinomas and 47 squamous cell carcinomas). This novel immunohistochemical marker showed high sensitivity and specificity when compared to conventional NE markers. Furthermore, our molecular biological experiments revealed that INSM1 was a critical upstream regulator of the NE differentiation pathway in SCLC cell lines. The elucidation of the significance of INSM1 expression in lung cancer strongly supports the diagnosis of NE tumours of the lung and promotes the understanding of the molecular biology of these tumours.

Keywords: Insulinoma-associated protein 1, Neuroendocrine Tumours of the Lung, small cell lung cancer

MA11.05 A CASE-CONTROL STUDY TO TEST THE USE OF CTDNA IN THE EARLY DETECTION OF SCLC REVEALS TP53 MUTATIONS IN NON-CANCER CONTROLS

Lynnette Fernandez-Cuesta1, Sandra Perdomo1, Patrice Avogbe2, Noémie Leblay3, Tiffany Delhomme3, Behnoush Abedi-Ardekan1, Estelle Chanudet1, Magali Olivier1, David Zaridze1, Anush Mukeria1, Graham Mckay1, Tiffany Delhomme1, Lynnette Fernandez-Cuesta1, Graham Mckay1, Magali Olivier1, David Zaridze1
1Department of Oncology, INSERM IARCbioinfo/needlestack, Lyon/France,
2Division of Thoracic Surgery, Hospital General, Costa Rica,
3Service d’oncologie Thoracique, CHU de Grenoble, Grenoble/France

Background: Circulating tumor DNA (ctDNA) is emerging as a key potential biomarker for post-diagnosis surveillance but it may also play a crucial role in the detection of pre-clinical cancer. Small-cell lung cancer (SCLC) is an excellent candidate for early detection given there are no successful therapeutic options for late-stage disease, and it displays universal sensitivity to chemotherapy and radiation.

Methods: We sequenced the DNA extracted from the white-blood cells (WBC) of 39 cfDNA TP53-positive patients, from which material was available (19 cases and 20 controls). Four cfDNA TP53 mutations (1 case and 3 controls) were detected in the WBC DNA, with similar AFs to those found in the cfDNA. There were no AFs below 1%, suggesting a somatic context for both the cfDNA and WBC DNA.

Conclusion: The detection of TP53 mutations in 11% of the 225 non-cancer controls suggests that somatic mutations in cfDNA among individuals without any cancer diagnosis is a common occurrence, and poses serious challenges for the development of ctDNA screening tests for the early diagnosis of cancer (Fernandez-Cuesta, Perdomo, and Avogbe 2016). We will discuss these results as well as follow-up analyses in retrospective and prospective series.

Keywords: TP53, ctDNA, Early Detection, SCLC

MA11.06 SWOG 0124: PLATINUM-SENSITIVITY STATUS AND POST-PROGRESSION SURVIVAL IN PATIENTS WITH EXTENSIVE-STAGE SMALL CELL LUNG CANCER

Primo Lara1, Jieling Miao2, James Moon3, Mary Redman4, David R. Gandara5, Kevin Kelly3
1UC Davis Comprehensive Cancer Center, Sacramento/CA/United States of America,
2Swog Statistical Center, Seattle/WA/United States of America,
3Swog Statistical Center, Seattle/United States of America,
4Division of Hem-Oncology, UC Davis Comprehensive Cancer Center, Sacramento/CA/United States of America,
5Hematology Oncology, UC Davis Comprehensive Cancer Center, Sacramento/CA/United States of America

Background: Patients with extensive stage small cell lung cancer (ES-SCLC) who progress after frontline platinum-based chemotherapy are often considered “platinum-sensitive” (progression > 90 days from last platinum dose) or “platinum-refractory” (progression < 90 days), as each group reportedly has differential overall survival (OS) outcomes. In a pooled analysis of recent SWOG trials of second and/or third-line targeted therapy, we showed that platinum-sensitivity status may no longer be as strongly associated with OS (Lara et al, JTO 2015). We assessed post-progression survival (PPS) following frontline platinum-based therapy in the context of ES-SCLC. We examined OS in ES-SCLC patients treated on SWOG 0124, a phase III trial of irinotecan/cisplatin vs etoposide/cisplatin. Methods: Data from 657 patients enrolled in S0124 were pooled. PPS was calculated as OS from the reported progression date. Crude PPS was evaluated using survival analysis (S-L method) for patients with platinum-sensitivity status in ES-SCLC.

Results: Of 657 patients, 534 had a progression date and thus included in the analysis: 162 (25%) were platinum-sensitive and 372 (75%) platinum-refractory. Fewer patients with PS 0 (32% vs. 41%) and more patients with weight loss > 5% (40% vs. 31%) were seen in the refractory group. Crude unadjusted PPS was higher in platinum-sensitive vs refractory patients (median PPS 7.5 vs. 4.3 months; HR=1.64, p=0.001). Multivariable Cox Proportional Hazard models were used to adjust for age, sex, smoking status, and baseline clinical covariates (i.e., measured at the time of first line therapy). After adjusting for these covariates, platinum-sensitive status was significantly associated with longer PPS (HR=1.87, p=0.001).
MA11.07 IMPROVED SMALL CELL LUNG CANCER (SCLC) RESPONSE RATES WITH VELIPARIB AND TEMOVULOMIZIDE: RESULTS FROM A PHASE II TRIAL

Lauren Averett Byers1, Lee Krug1, Saimaa Waqar1, Afsin Dowlati2, Christine Hann1, Alberto Chiappori3, Taofeeq Owonikoko1, Kaitlin Wool1, Yevgeniya Bensman1, Brenda Hurtado2, Robert Cardnell1, Lixia Diao1, Youfang Hon1, Junya Fujimoto1, Jaime Rodriguez-Canales5, Ihong Long1, Erik Sullman1, Ignacio Wistuba1, Jing Wang1, William Travis1, Alice Chen1, Charles Rudin1, Mark Kris1, Martin Fleisher2, John Hayman3, Glen Weiss4, Christos Antoniou5,

1Thoracic/Head & Neck Medical Oncology, University of Texas MD Anderson Cancer Center, Houston/TX/United States of America, 2Department of Pathology, Memorial Sloan Kettering Cancer Center, New York/NY/United States of America, 3Division of Thoracic Medicine, Memorial Sloan Kettering Cancer Center, New York/NY/United States of America, 4Dept of Pathology, Memorial Sloan Kettering Cancer Center, New York/NY/United States of America, 5Division of Cancer Treatment and Diagnosis, National Cancer Institute, Bethesda/MD/United States of America, 6Dermatology, University of Texas MD Anderson Cancer Center, Houston/TX/United States of America, 7Radiation Oncology, University of Texas MD Anderson Cancer Center, Houston/TX/United States of America, 8Depot of Pathology, Memorial Sloan Kettering Cancer Center, New York/NY/United States of America, 9Division of Cancer Treatment and Diagnosis, National Cancer Institute, Bethesda/MD/United States of America, 10Medicine, Memorial Sloan Kettering Cancer Center, New York/NY/United States of America, 11Thoracic Oncology, Memorial Sloan Kettering Cancer Center, New York/NY/United States of America

Background: PARP1 is overexpressed in small cell lung cancer (SCLC) and represents a novel therapeutic target for this disease. Preclinical data indicates that combining veliparib (an oral PARP-1/2 inhibitor) and temovulomizide (TMZ) results in synergistic tumor growth delay or regression. In this study, we investigated whether adding veliparib to TMZ would improve outcomes in patients with relapsed sensitive and refractory SCLCs. Candidate predictive biomarkers, including SLFN11, were then explored. Methods: SCLC patients previously treated with 1 or 2 prior regimens were enrolled in the trial and randomized 1:1 to receive oral TMZ 150-200mg/m2/day (D1-5) with either veliparib or placebo 40mg twice daily, orally (D1-7) (NCT01638546). Primary endpoint was 4-month progression free survival (PFS). Data were analyzed in patients with platinum sensitive (progression >60 days after 1st line therapy) or refractory disease (progression ≤60 days after 1st line therapy, or in need of 3rd line treatment). Archived tissue was available for 53 patients for biomarker analysis. Results: 104 patients were enrolled and 100 patients were treated. Baseline characteristics were balanced between treatment arms. 52% female, median age 62.5 (range, 31-84); 59% platinum-sensitive disease; 33% needing 3rd-line therapy. Progression free survival at 4-months was similar between the two arms, 36% vs. 27% (p=0.39). However, in 93 evaluable pts, response rate was significantly higher in pts treated with veliparib/TMZ compared to TMZ alone (39% vs 16%, p=0.016). Median on treatment survival was 8.2 mos (95% Cl: 6.4-12.2) in veliparib arm and 7 mos (95% Cl: 5.3-9.5) in placebo arm, p = 0.50. Grade 3/4 thrombocytopenia and neutropenia more commonly occurred in the veliparib/TMZ arm: 50% vs 9% and 31% vs 7%, respectively. Levels of SLFN11, a marker of SCLC response to PARP inhibition in preclinical models, were assayed by immunohistochemistry. High SLFN11 levels were associated with sensitivity to PARP inhibitors (p=0.03). Conclusion: By incorporating changes after the first cycle (i.e. from baseline to the end of cycle 1) and in between cycles (i.e. end of cycle 1 to end of cycle 2), we were able to identify patients with non-progression disease. This might reduce the need for interim CT scans. References: 1. Muley, et al. Journal of Thoracic Oncology 2015; 10(9) Supplement 2:MINI27.13

Keywords: SCLC, ProGRP

MA11.09 PROGASTRIN-RELEASING PEPTIDE (PROGRP) TO RULE OUT PROGRESSIVE DISEASE IN PATIENTS WITH SMALL CELL LUNG CARCINOMA (SCLC)

Thomas Muley1, Xiaoguang Zhang1, Stefan Holdenrieder2, Catharina Korsse1, Xiuyi Zhu1, Rafael Molina1, Zhihong Zou1, Ulrike Hartmann1, Michel Van Den Heuvel1, Kun Qian1, Ramon Marrades3, Christine Engel1, Ying He1, Birgit Wehn1, Farshid Dayash1, Felix J Herth1,2

1Translational Research Unit (St), Translational Lung Cancer Research Center Heidelberg (TLRC), Member of the German Center for Lung Research (DZL), Thoraxklinik at Heidelberg University, Heidelberg/Germany, 2Heidelberg/Germany, 3Peking Union Medical College Hospital (PUMCH), Beijing/China, 4University of Bonn, Bonn/Germany, 5The Netherlands Cancer Institute, Amsterdam/Netherlands, 6Xuanwu Hospital, Capital Medical University, Beijing/China, 7Hospital Clinic, University of Barcelona, Barcelona/Spain, 8Roche Diagnostics GmbH, Penzberg/Germany, 9Roche Diagnostics International, Rotkreuz/Switzerland

Background: For patients with SCLC, response to chemotherapy is monitored by computed tomography (CT) scans, which can be costly and inconvenient. A previous study showed that baseline levels (>100 pg/ml) of the tumor marker, ProGRP, were positively correlated with advanced SCLC, and a decline in ProGRP levels after two cycles of chemotherapy was associated with a trend towards better overall survival in the veliparib/TMZ arm, but no difference in outcome in the placebo arm. The aim of our study was to evaluate whether baseline ProGRP levels could be used to rule out progressive disease in patients with SCLC. Methods: Patients with SCLC receiving first-line platinum-based doublet chemotherapy or a single-agent cytotoxic agent were included in this study. Patients with SCLC with elevated baseline ProGRP levels (>100 pg/ml) were excluded. A logistic regression model was calculated to incorporate changes after the first cycle (i.e. from baseline to the end of cycle 1) and in between cycles (i.e. end of cycle 1 to end of cycle 2). Results: Of 156 patients, 85 patients met the study criteria. The majority of patients were male (78%), and 84% had not received prior treatment. Among the 85 patients, 76% had a baseline ProGRP level >100 pg/ml. The AUC for the change in ProGRP level from baseline to the end of cycle 1 was 0.76 (95% CI: 0.63-0.88). When using a cutoff of 100 pg/ml, the sensitivity and specificity of the model were 70.4% and 83.7%, respectively. Conclusion: The ProGRP assay can be used as a cost-effective tool to rule out progression after the first cycle in patients with advanced SCLC. However, the cut-off levels of baseline and cycle 1 ProGRP levels need to be validated in a larger multicenter study. References: 1. Muley, et al. Journal of Thoracic Oncology 2015; 10(9) Supplement 2:MINI27.13

Keywords: SCLC, ProGRP

MA11.10 PROSPECTIVE STUDY OF GENOME-WIDE STREXOME AND TRANSCRIPTOME PROFILING IN PATIENTS WITH SMALL CELL LUNG CANCER PROGRESSING AFTER 1ST LINE THERAPY

Glen Weiss1, Ashish Sangal1, Heather Barilla1, Sara Byron1, Jeff Kiefer1, Jessica Aldrich1, Timothy Whitsett1, John Carpent1, David Craig1

1Western Regional Medical Center, Cancer Treatment Centers of America, Goodyear/AZ/United States of America, 2Translational Genomics Research Institute, Phoenix/AZ/United States of America

Background: Small cell lung cancer (SCLC) that has progressed after 1st line therapy has few effective treatments and no new class of approved therapies in over 20 years. Paired tumor-normal exome and transcriptome sequencing was performed on paired tumor-normal exomes and RNA-seq libraries from patients who progressed after 1st line therapy and underwent expression changes in advanced SCLC and attempt to prescribe systemic therapy based on the results (NCT02297087, study funded by SU2C). Methods: After informed consent a prospective fresh frozen tumor biopsy was obtained. Germline DNA was extracted from PBMC and reference normal tissue RNA was obtained commercially. Strain and RNA-seq libraries were prepared and NGS, data analysis, and reporting were performed in a CLIA-certified CAP accredited environment. Results: The study completed its accrual goal of 12 evaluable patients. There was one screen failure due to anticipated inadequate sample yield because of tumor location. The cohort included 9 males and 3 females with a median age of 62 years (range, 41-79) and 82% of patients were current or past smokers. All patients were platinum-refractory and 83% had a smoking history. Conclusions: The SCLC genome-wide strexome and transcriptome project investigated patients progressing after 1st line therapy and will be available at the time of abstract presentation. The results may identify new therapeutic targets for SCLC.
MA11: NOVEL APPROACHES IN SCLC AND NEUROENDOCRINE TUMORS
TUESDAY, DECEMBER 6, 2016 - 14:15-15:45

MA11.115 HIPPOCAMPAL AVOIDANCE DURING WHOLE BRAIN RADIOThERAPY RISKY FOR SMALL CELL LUNG CANCER PATIENTS?
Esra Kirakli1, Özgur Oztekin
1Radiation Oncology, Dr. Sait Seren Göğüş Hastalıkları Ve Cerrahisi Eğitim Ve Araştırma Hastanesi, İzmir/Turkey

Background: Hippocampal avoidance (HA) during whole brain radiotherapy (WBRT) is performed to prevent neural stem-cell injury causing decreased neurocognitive function. Nevertheless, the estimated risk for metastases in HA area in small cell lung cancer (SCLC) patients is unknown. The current study aimed to characterize the metastatic distribution within the brain relative to the hippocampus and estimate the incidence of hippocampal metastasis. SCLC patients and also identify clinical and radiographic variables that may be associated with the presence of metastases within the HA area. Methods: SCLC patients treated with WBRT between January 2010 and December 2015 were reviewed. T1-wighted, post-contrast axial MRI (1.5 or 3 Tesla) images obtained just before therapeutic cranial irradiation were retrieved and reviewed for each patient. The HA area was generated by expanding the hippocampal contour by 5 mm volumetrically to account for necessary dose fall-off between the hippocampus (HP) and the whole brain planning target volume. Metastatic lesions within HP or HA area were defined as HP metastasis. HP metastasis rate was evaluated and characteristics of patients with HP metastasis were analyzed and compared to patients without HP metastasis. Results: 54 patients evaluated with cranial MRI were enrolled. HP metastasis rate was 32% (17 patients). 4.4% of all metastases involved the HP and HA area (2.2% of metastases each)

The most common location of metastasis was frontal lobe followed by cerebellum and temporal lobe. Having diabetes mellitus (OR: 12.1, 95% CI: 1.1-137.4, p=0.045) and being younger than 65 years of age (OR: 4.8, 95% CI: 1.23-2.2, p=0.049) were found to be independent risk factors for HP metastasis.

Keywords: small cell lung cancer, clinical trials, whole transcriptome sequencing, next-generation sequencing

MA12.01 NEXT GENERATION SEQUENCING BASED CLINICAL FRAMEWORK FOR ANALYSES OF TREATMENT PREDICTIVE MUTATIONS AND GENE FUSIONS IN LUNG CANCER
Kajsa Ericson Lindquist1, Annar Karlsson1, Per Lövêén1, Hans Brunstrom1, Christel Reuswold1, Karolina Holmir1, Mats Jonsson1, Karin Annersten2, Frida Rosengren2, Karin Jirström2, Jaroslav Kosiarek2, Lars EK1, Åke Borg2, Maria Planck2, Göran Jonsson1, Johan Staa2
1Pathology, Regional Laboratories Region Skåne, Lund/Sweden, 2Oncology and Pathology, Lund University, Lund/Sweden, 3Department of Respiratory Medicine and Allergology, Skane University Hospital, Lund/Sweden

Background: The use of new, emerging techniques in the search of tailored patient therapies is rapidly becoming a reality. Here we describe the optimization and implementation of next generation sequencing for treatment predictive mutation screening in parallel with gene fusion status of ALK, RET and ROS1 in non-small cell lung cancer (NSCLC) patients.

Methods: The Illumina TruSight tumor 26-gene NGS panel was validated in 81 clinical routine FFPE or cytology specimens and implemented in 153 diagnostic NSCLCs during one year of clinical analysis. In parallel, a RNA-based NanoString method was evaluated in 169 cases for gene fusion status of ALK, RET and ROS1. Results: We have successfully established a streamlined workflow with a 5-day turnaround time from specimen arrival to mutation report. The concordance in the validation cohort was 99% for comparable variants. In the 533 diagnostic samples, 12 variants were detected in 79% of the cases. Most frequently mutated genes included TP53, KRAS, EGFR, STK11, and BRAF, all with differences in mutational patterns between histological subgroups. The RNA-based NanoString assay was successfully established and validated. The success rate in the 169 cases was 80% and 10 gene fusions were found (five ALK fusions, three RET fusions and two ROS1 fusions) in all adenocarcinomas. Integration of mutation and gene fusion status revealed that 68% of adenocarcinomas, 13% of SqCCs and 56% of NSCLC-NOS harbored ≥1 alterationable action ALK, RET, ROS1, EGFR, KRAS, PIK3CA, BRAF, NRAS, MAP2K1, ERBB2 or AKT1. Specifically, in 13.2% of the adenocarcinomas, where no EGFR or ALK alteration was detected emerging targeted therapy may be considered in addition to the 15.3% of patients that was eligible for EGFR or ALK inhibitors. The corresponding proportions for SqCCs were 5.5% in addition to the 2.2%, and for NSCLC-NOS 2.5% in addition to the 11.2% eligible for EGFR or ALK inhibitors. Conclusion: Next generation sequencing in combination with the NanoString technology is time- and cost-efficient in the diagnostic routine for treatment predictive mutation screening and gene fusion status detection. The techniques represent valuable tools for pinpointing patient eligible to standard targeted therapies in addition to new emerging therapies.

Keywords: NGS, clinical routine, mutation, personalized medicine

MA12.02 MMP12 AND LMO7, TWO KEY PLAYERS ON OPPOSITE SIDES OF EARLY LUNG SQUMOUS CELL CARCINOMA DEVELOPMENT
Angela Barrett1, Sofia Lourenco1, Krishna Kolluri1, Bernadette Carroll1, Mary Falzon1, Elaine Borg1, Jeremy George2, Sam Janes1, Vitor Teixeira1
1Medical, University College London, London/United Kingdom, 2University College London Hospital, London/United Kingdom, 3Lungs for Living Research Centre, UCL Respiratory, University College London, London/United Kingdom

Background: Our laboratory has a unique cohort of patients with pre-invasive lung squamous cell carcinoma (SqCC) lesions, within which there is a clear discrepancy between the prevalence of pre-invasive lesions and the incidence of lung cancer, suggesting that not all pre-invasive lesions progress to cancer. Using gene expression microarrays we identified 1846 genes significantly differentially expressed between progressive and regressive pre-invasive SqCC lesions. The macrophage metalloelastase MMP12 gene was found to be highly expressed in progressive lesions, and we hypothesised that it
MA12.04 MITOCHONDRIAL-RELATED PROTEINS, PGAMS AND FUNDC1, IN COPD-ASSOCIATED NON-SMALL CELL LUNG CARCINOMA
Francois Kwong1, Andrew Nicholson1, Ian Adcock2, Fan Chung2
1Histopathology, Royal Brompton and Harefield NHS Foundation Trust, London/United Kingdom, 2National Heart and Lung Institute, London/United Kingdom, 3Experimental Studies, National Heart and Lung Institute, London/United Kingdom

Background: Patients with COPD and/or emphysema have an increased risk of non-small cell lung cancer (NSCLC). COPD and lung cancer are both characterised by increased oxidative stress associated with mitochondrial dysfunction. We hypothesise that mitochondrial dysfunction is a driving mechanism for the increased risk of NSCLC in COPD. We determined whether there is dysregulated expression of mitochondrial-related proteins in NSCLC arising in COPD, and if so, their clinical significance. Methods: To determine the clinical relevance of mitochondrial related gene expression, we examined a database containing transcriptomic data of more than 1,000 human NSCLC samples and with survival outcomes (https://precog.stanford.edu/).

Immunohistochemistry for PGAMS and FUNDC1 was performed on cancer and background (‘normal’) tissue from lung cancer resections from non-smokers, healthy smokers (without COPD) and COPD/emphysema patients. Protein expression was assessed using a semi-quantitative immunohistochemical scoring system (H score). Specific gene expression was further correlated with outcome in dataset GSE72194, containing transcriptomic data of NSCLC cases and patient survival. Results: 25 mitochondrial-related genes were linked to survival in NSCLC. Of those 25, we chose to study further the expression of PGAMS (PGAM2 and PGAM3) and FUNDC1, which are regulators of mitochondrial degradation (mitophagy). In background lung tissue, PGAMS and FUNDC1, only expressed in alveolar macrophages, were most highly expressed in COPD (H score: 180 ± 58 and 23 ± 9, respectively) compared to healthy smokers (146 ± 58 and 20 ± 8) and non-smokers (68 ± 48 and 3.3 ± 1.4) (p<0.001). In cancerous tissue, the malignant epithelial cells and associated macrophages, as well as the periphery of the cancer, expressed PGAMS and FUNDC1. PGAMS was also expressed in pre-neoplastic epithelium (squamous dysplasia and carcinoma in situ). There was no difference in expression across the 3 groups, although compared with healthy smokers, at the edge of cancer, from COPD patients tended to show significantly small expression. Conclusion: The expression of PGAMS and FUNDC1 may contribute to the pathogenesis of both COPD and NSCLC, possibly through mitophagic processes.

Keywords: copd, mitochondrion, macrophages, Cancer

MA12.05 CAN TUMOR SPREAD THROUGH AIR SPACES (STAS) IN LUNG ADENOCARCINOMAS BE PREDICTED PRE- AND INTRAOPERATIVELY?
Kooi Kameda1, Shaohua Lu1, Takashi Eguchi2, Natasha Rekhtman2, Jason Chang3, Joseph Montecalvo2, David Jones1, William Travis1, Prasad Adusumilli2
Thoracic Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York/United States of America, 2Department of Pathology, Memorial Sloan Kettering Cancer Center, New York/United States of America

Background: We and others have reported the prognostic impact of tumor spread through air spaces (STAS) in lung adenocarcinomas. The goal of this study is to investigate preoperative predicting factors for STAS and to determine whether STAS can be detected by intraoperative frozen section analysis. Methods: In a cohort of 874 patients with small (≤2cm) stage I adenocarcinoma (1995-2012), we reviewed preoperative computed tomography (CT) and positron emission tomography (PET) scans. According to the 2016 Fleischner Society’s criteria, radiological whole tumor size, consolidation size, as well as C/T ratio (consolidation/whole tumor diameter) were determined using thin slice (<3mm) CT scans where available (n=176). Clinico-radiological prediction of STAS was evaluated by logistic regression model. Using the frozen section slides with adequate adjacent lung parenchyma surrounding tumor without artifact (n=48), the presence of STAS was evaluated by five pathologists who are unaware of the radiological findings or the pathological information on permanent slides. The kappa statistic was calculated to measure the agreement between two pathologists.

Results: In univariable model for predicting STAS, current smoker, larger consolidation size, C/T ratio, and SUVmax were significant variables. In multivariable model, current smoker and C/T ratio were independent risk factors for the presence of STAS (p=0.027 and p<0.001, respectively). The sensitivity and the specificity of frozen section for prediction of STAS were 71% (95% confidence interval: 52-91%), 92.4% (81-100%) respectively, and the accuracy was 80% (71-89%). The kappa statistics were 0.40-0.74 (Table 1b) with B/10 being moderate or substantial agreement.

Conclusion: Smoking status and C/T ratio were independent predictors for the presence of STAS in patients with small lung adenocarcinomas. Frozen section prepared with adequate surrounding normal lung tissue may help identify STAS intraoperatively.

Keywords: smoking, diagnosis, computed tomography, radiology

Table 1a. Preliminary univariable and multivariable analysis for predicting STAS

<table>
<thead>
<tr>
<th>Preoperative variables</th>
<th>Univariable</th>
<th>Multivariable</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds ratio</td>
<td>95% C.I.</td>
</tr>
<tr>
<td>Age (per 1-year increase)</td>
<td>1.00</td>
<td>0.97 - 1.03</td>
</tr>
<tr>
<td>Sex (Male vs Female)</td>
<td>1.00</td>
<td>0.95 - 1.05</td>
</tr>
<tr>
<td>Smoking (Current vs Never/Former)</td>
<td>1.00</td>
<td>0.95 - 1.05</td>
</tr>
<tr>
<td>Pack-year (per 1 pack-year increase)</td>
<td>1.00</td>
<td>0.95 - 1.05</td>
</tr>
<tr>
<td>Total tumor size (cm) (per 1 cm increase)</td>
<td>0.97</td>
<td>0.57 - 1.65</td>
</tr>
<tr>
<td>Consolidation size (cm) (per 1 cm increase)</td>
<td>0.97</td>
<td>0.57 - 1.65</td>
</tr>
<tr>
<td>C/T ratio (%) (per 1% increase)</td>
<td>1.02</td>
<td>1.02 - 1.04</td>
</tr>
<tr>
<td>SUVmax (per 1 SUV increase)</td>
<td>1.12</td>
<td>1.07 - 1.15</td>
</tr>
</tbody>
</table>

Table 1b. Interobserver agreement for STAS on frozen section sides

<table>
<thead>
<tr>
<th>Pathologists</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strength of Kappa statistic</td>
<td>Slight</td>
<td>Fair</td>
<td>“Moderate”</td>
<td>“Substantial”</td>
<td>Almost</td>
</tr>
<tr>
<td>1</td>
<td>0.60 (p=0.02)</td>
<td>0.24 (p=0.40)</td>
<td>0.41 (p=0.06)</td>
<td>0.61 (p=0.80)</td>
<td>0.81 (p=1.00)</td>
</tr>
<tr>
<td>2</td>
<td>0.49 (p=0.04)</td>
<td>0.52 (p=0.05)</td>
<td>0.61 (p=0.80)</td>
<td>0.81 (p=1.00)</td>
<td>0.81 (p=1.00)</td>
</tr>
<tr>
<td>3</td>
<td>0.61 (p=0.02)</td>
<td>0.60 (p=0.02)</td>
<td>0.71 (p=0.01)</td>
<td>0.82 (p=0.001)</td>
<td>0.82 (p=0.001)</td>
</tr>
<tr>
<td>4</td>
<td>0.63 (p=0.01)</td>
<td>0.64 (p=0.01)</td>
<td>0.74 (p=0.001)</td>
<td>0.85 (p=0.001)</td>
<td>0.85 (p=0.001)</td>
</tr>
<tr>
<td>5</td>
<td>0.65 (p=0.01)</td>
<td>0.66 (p=0.01)</td>
<td>0.77 (p=0.001)</td>
<td>0.88 (p=0.001)</td>
<td>0.88 (p=0.001)</td>
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COMPETING RISK ANALYSIS

SQUAMOUS CELL CANCER IS AN INDEPENDENT RISK FACTOR: A COMPETING RISK ANALYSIS

Shaohua Lu1, Takashi Eguchi2, Kay See Tan1, Sarina Bains3, Kyuichi Kadota4, Natasha Rekhtman5, Prasad Adusumilli1, William Travis1

1Department of Pathology, Memorial Sloan Kettering Cancer Center, New York/NY/United States of America, 2Thoracic Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York/NY/United States of America, 3Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York/NY/United States of America, 4Dept of Pathology, Memorial Sloan Kettering Cancer Center, New York/NY/United States of America

Background: Tumor spread through air spaces (STAS) is a recently recognized pattern of invasion in lung adenocarcinoma, however, the incidence and prognostic importance of STAS have not yet been defined in squamous cell carcinoma (SCC).

Methods: In a cohort of 445 patients with p-stage I-III lung SCC, incidence of recurrence and lung cancer-specific death (LCSD) was evaluated by competing risks analysis and overall survival (OS) by Cox models. Results: 76% of patients were ≥65 years of age. 273 patients died during follow-up, one third (31, 33.3%) died of lung cancer whereas two thirds died of competing events or unknown cause. STAS was present in 132 (30%). The cumulative incidence of any, distant, and locoregional recurrence as well as LCSD were significantly higher in patients with STAS compared to those without STAS (Figure), whereas there was no statistically significant difference in OS, STAS was an independent predictor for both recurrence and LCSD in multivariable analysis (p=0.034 and 0.016, respectively, Table).

Conclusion: STAS was present in one third of resected lung SCC and it was an independent predictor of recurrence and LCSD, supporting our proposal that STAS is a clinically important pattern of invasion and not an artifact.

Keywords: Lung cancer-specific death, Lung Squamous cell carcinoma, invasion, Tumor spread through air spaces


table: Multivariable competing-risk regression model for any recurrence and lung cancer-specific death

<table>
<thead>
<tr>
<th>Variable</th>
<th>Any recurrence</th>
<th></th>
<th>Lung cancer-specific death</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>subHR</td>
<td>95% CI</td>
<td>subHR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Sex: female vs. male</td>
<td>1.53</td>
<td>1.01, 2.32</td>
<td>0.043</td>
<td>0.3, 0.54</td>
</tr>
<tr>
<td>Smoking pack-year &gt;90 vs ≤90</td>
<td>1.95</td>
<td>0.86, 5.56</td>
<td>0.059</td>
<td>1.93, 4.33</td>
</tr>
<tr>
<td>Pathological stage (vs Stage I)</td>
<td>1.55</td>
<td>0.95, 2.32</td>
<td>0.11</td>
<td>1.23, 5.69</td>
</tr>
<tr>
<td>Stage II</td>
<td>1.95</td>
<td>0.86, 5.56</td>
<td>0.059</td>
<td>1.93, 4.33</td>
</tr>
<tr>
<td>Stage III</td>
<td>1.95</td>
<td>0.86, 5.56</td>
<td>0.059</td>
<td>1.93, 4.33</td>
</tr>
<tr>
<td>Tumor size: ≤1 vs &gt;1 cm</td>
<td>1.95</td>
<td>0.86, 5.56</td>
<td>0.059</td>
<td>1.93, 4.33</td>
</tr>
<tr>
<td>Lymphatic invasion: present vs. absent</td>
<td>1.25</td>
<td>0.8, 6.39</td>
<td>0.059</td>
<td>1.23, 5.69</td>
</tr>
<tr>
<td>Vascular invasion: present vs. absent</td>
<td>1.25</td>
<td>0.8, 6.39</td>
<td>0.059</td>
<td>1.23, 5.69</td>
</tr>
<tr>
<td>Necrosis: present vs. absent</td>
<td>1.19</td>
<td>0.99, 2.07</td>
<td>0.060</td>
<td>1.07, 2.22</td>
</tr>
<tr>
<td>Nuclear size: large vs. small</td>
<td>1.19</td>
<td>0.99, 2.07</td>
<td>0.060</td>
<td>1.07, 2.22</td>
</tr>
<tr>
<td>Tumor budding: &lt;1 vs ≥1</td>
<td>1.19</td>
<td>0.99, 2.07</td>
<td>0.060</td>
<td>1.07, 2.22</td>
</tr>
<tr>
<td>Single cell invasion: present vs. absent</td>
<td>1.19</td>
<td>0.99, 2.07</td>
<td>0.060</td>
<td>1.07, 2.22</td>
</tr>
<tr>
<td>STAS: present vs. absent</td>
<td>1.19</td>
<td>0.99, 2.07</td>
<td>0.060</td>
<td>1.07, 2.22</td>
</tr>
</tbody>
</table>

CI, confidence interval; HR, hazard ratio; subHR, subhazard ratio; STAS, spread through air spaces

* variables with p-value ≤0.1 in univariable models were not analyzed in multivariable model
MA12.09 COMPARATIVE HISTOLOGICAL SUBTYPE ANALYSIS OF LUNG ADENOCARCINOMA TUMOR AND METASTATIC LYMPH NODES AND THE PROGNOSTIC IMPACT

Shaohua Lu1, Takashi Eguchi2, Zachary Tano2, Daniela Molena2, David Jones2, William Travis1, Prasad Adusumilli2

1Department of Pathology, Memorial Sloan Kettering Cancer Center, New York/NY/United States of America, 2Thoracic Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York/NY/United States of America

Background: The goal of this study is to investigate comprehensive comparative pathological analyses of both primary tumor and metastatic lymph node (LN) and correlate with lung cancer-specific death (LC-death) in patients with LN-positive lung adenocarcinoma. Methods: PNI2 lung adenocarcinoma patients who underwent R0 resection without induction therapy (n=402, 2000-2012) were included in the study. In primary tumor, lymphatic/vascular/pleural invasion, necrosis, tumor spread through air spaces (STAS), as well as histologic subtypes according to 2015 WHO classification were evaluated. In metastatic LN, metastatic tumor size, extracapsular invasion, histologic subtypes were evaluated. Recurrence and LC-death were analyzed by Cox model. Results: Micropapillary and solid predominant subtypes were more frequent in LN metastases than in primary tumors (Figure). In multivariable analyses, adjuvant chemotherapy, pleural invasion, extracapsular invasion of LN metastasis, micropapillary predominant subtype in LN metastasis were independent factors for recurrence; adjuvant chemotherapy, pleural invasion, tumor STAS, and extracapsular invasion were for LC-death (Table). Conclusion: In lung adenocarcinoma lymph node metastases, predominant micropapillary pattern and extracapsular invasion indicate high risk for recurrence and lung cancer-specific death.

MA12.10 HISTOLOGICAL SUBTYPING OF MATCHED PRIMARY AND METASTASES SITES IN LUNG ADENOCARCINOMA: SIGNIFICANCE OF SOLID PREDOMINANCE

Yusuke Takahashi1, Takashi Eguchi1, Shaohua Lu1, Robert Downey1, David Jones1, William Travis3, Prasad Adusumilli2

1Thoracic Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York/NY/United States of America, 2Department of Pathology, Memorial Sloan Kettering Cancer Center, New York/NY/United States of America

Background: Clinical significance of 2015 WHO classification histological subtype of early-stage lung adenocarcinoma (LADC) has been well documented; the incidence and significance of histological subtypes in autologous metastatic tumors is unknown. Methods: Histological subtyping was performed on paired primary and metastatic LADC tumor samples from patients who underwent resection of metastases (N=203, 1996-2012). 57 cases with inadequate tumor specimen and 4 cases diagnosed as local recurrence were excluded. Results: Location of metastatic sites were - brain 51 (35.9%), lung 48 (33.8%), lymph node 14 (9.9%), pleura 10 (7.0%), and adrenal gland 5 (3.5%). Metastatic tumors demonstrated more frequent solid histological pattern than primary tumors (first predominance: 51% vs. 24%; second predominance 29% vs. 17%, Figure 1). In addition, analysis of all available clinicopathological factors showed significantly higher percentage of solid subtype in both primary and metastatic tumors was observed in patients with smoking history (p=0.003 and p=0.004, respectively). Conclusion: Analysis of a large cohort of primary and autologous metastatic LADC tumors demonstrated a higher percentage of solid histological pattern metastases, even in cancers with a low solid component in the primary site of disease.
MAI3.01 MARKERLESS TUMOUR TRACKING DURING LUNG RADIOTHERAPY USING INTRACTION X-RAY IMAGING

Chun-Chieh (Andy) Shieh1, Vincent Caillet1, Michelle Dunbar2, Paul Keall1, Nicholas Hardcastle2, Jeremy Booth1, Chen-Yu Huang1, Carol Haddad2, Thomas Eade1, Ilana Feain1

1Radiation Physics Laboratory, University of Sydney, Sydney/NSW/Australia, 2Northern Sydney Cancer Centre, Royal North Shore Hospital, St Leonards/NSW/Australia

Background: Lung tumours often exhibit large and unpredictable motion that can severely compromise radiotherapy outcomes. Markerless tumour tracking can enable wide access to motion-adaptive radiotherapy, negating the risks and costs associated with implanting markers. The main barrier to markerless tumour tracking is the inferior tumor visibility on x-ray images due to overlapping anatomic structures. The aim of this study is to develop a markerless tumor tracking method for lung radiotherapy using intrafraction x-ray imaging. Methods: The markerless tumour tracking method (Figure1a) consists of four steps: (1) Building a tumour and anatomic model from the cone-beam CT (CBCT) acquired prior to treatment, (2) Using the anatomic model to remove the contribution of anatomic structures on intrafraction x-ray images, (3) Locating the tumour on the intrafraction 2D x-ray image via template matching using the tumour model, (4) Determining the tumour 3D position by a Kalman filter. The proposed method was retrospectively validated on (i) 11 CBCT scans from four patients with central tumours, and (ii) a kV fluoroscopic scan during a stereotactic ablative radiotherapy (SABR) treatment from the Light SABR trial (NCT02514512). Tracking errors were estimated using the motions of markers or beacons implanted near the tumours.

Results: Markerless tumour tracking successfully tracked tumours in all cases at every imaging angle. The mean 3D tracking error ranged from 1.8-4.1mm for the 11 CBCT scans, and was 3.0mm for the SABR case. Compared with the current standard of care, i.e. a single estimation of tumour position prior to treatment from the pre-treatment CBCT, markerless tumour tracking reduced tumour localization error by 0.9-7.9mm. Tracking errors in the left-right, superior-inferior, and anterior-posterior directions are shown in Figure1b.

Conclusion: A markerless tumour tracking method was developed and shown to improve tumour localization accuracy in 12 lung cancer cases. This method can potentially enable wide access to motion-adaptive radiotherapy.

Keywords: Tumor tracking, Intrafraction monitoring, Real-time adaptive radiotherapy, X-ray imaging

MAI3.02 FIRST-IN-HUMAN CLINICAL EXPERIENCE WITH REAL-TIME TUMOR TARGETING VIA MLC TRACKING FOR STEREOTACTIC RADIOTHERAPY OF LUNG CANCER

Jeremy Booth1, Vincent Caillet1, Nicholas Hardcastle1, Carol Haddad1, Kathryn Szymura1, Ricky O’Brien1, Benjamin Harris2, Thomas Eade1, Paul Keall2

1Northern Sydney Cancer Centre, Royal North Shore Hospital, St Leonards/NSW/Australia, 2University of Sydney, Sydney/NSW/Australia

Background: MLC tracking is an emerging technology to improve tumor targeting and reduce normal tissue irradiation during radiotherapy. The purpose of this work is to present the early clinical experience from the first-in-human trial of real-time tumor targeting via MLC tracking for stereotactic ablative body radiotherapy (SABR) of lung cancer. Methods: Full ethics approval through an Australian ethics board has been received for recruitment of 20 patients with stage I lung cancer or lung metastases into the MLC tracking clinical trial (NCT02514512). To date, seven recruited patients have each had three electromagnetic beacons inserted near the tumor. An MLC tracking SABR plan was generated with planning target volume (PTV) expanded 5mm from end-exhale tumor volume (GTV). For comparison a conventional motion-encompassing SABR plan was generated with PTV expanded 5mm from a 4DCT-derived internal target volume (ITV). Treatment was delivered using a standard linear accelerator using in-house developed software to continuously adapt the MLC motion based on the Calypso beacons’ movement. Tumor motion, treated volume and reconstructed delivered dose were compared between MLC tracking and conventional motion-encompassing treatment planning. Results: All seven patients have been treated successfully with MLC tracking (23 successful fractions). The MLC tracking PTV for all patients has been smaller than with ITV based planning (range 12% to 61% reduction, or 2 to 18 cm3 with MLC tracking). Subsequent reductions in normal lung dose were observed. Tumor motion was seen to vary in motion range from the planning 4DCT during treatment; significantly, larger motion was observed during treatment that exceeded standard PTV boundaries. Reconstruction of delivered treatments confirmed the accurate delivery of MLC tracking, with 100% prescribed dose delivered to the GTV. (See Figure next page)
MA13.03 ANALYSIS OF INTRA-THORACIC ANATOMICAL CHANGES OBSERVED IN CLINICAL WORKFLOW OF CONE-BEAM CT GUIDED RADIOTHERAPY FOR LUNG CANCER
José Belderbos, Maddalena Rossi, Margriet Kwint, Suzanne Beek, Jan-Jakob Sonke

Background: Objectives: In lung cancer patients treated with image-guided radiotherapy we use daily Cone-Beam CT (CBCT) guidance for setup verification and to check on intra-thoracic anatomical changes (ITACs). ITACs like tumor baseline shifts, the occurrence or dissolving of an atelectasis, tumor progression or regression, pleural fluid- and infiltrative changes have been reported in 72% of lung cancer patients (Kwint M R&O 2014) during the course of irradiation. A traffic light protocol has been in use by the radiation technologists since 2010 to classify anatomical changes seen on the CBCT with anticipated different influences on the dose distribution using a 4 action levels. The purpose of this study was to quantify how often the ITACs occurred in daily clinical practice and for which action level. Methods: All lung cancer patients irradiated in 2015 (excluding stereotactic treatments) with a dose >44 Gy were included. All patients had a daily CBCT guided online correction protocol and the traffic light action level of each CBCT was recorded. The following action levels have been defined: code red for immediate consultation with the physician before beam-on, code orange for a decision on the notification of the physician before the next fraction, code yellow to inform the physician; no action is required- and green for no change so no intervention necessary. We also analyzed the percentage of patients that received a new planning CT-scan and/or a new treatment plan. Results: In 2015 a total of 299 lung cancer patients were conventionally irradiated with radical intent and 5971 CBCT scans were made. Of these CBCTs 51% were scored as code green, 24% as code yellow, 24% as code orange and code red in less than 1% of the CBCTs. Forty patients (13%) had a new treatment plan, of which 34 patients (11%) had a new planning CT-scan and 6 patients (2%) had a new treatment plan on the original planning CT-scan. Conclusion: Image-guided irradiation for 299 conventionally fractionated lung cancer patients (~44 Gy) in 2015 revealed ITACs in 25% of the CBCT's made and a physician's decision on the notification was necessary. At a total of 13% of the patients treated received an unscheduled adaptive treatment plan during the course of treatment. The traffic light protocol in daily clinical workflow worked well as a tool to prioritize a physician's decision based on the ITACs seen on the CBCT images. Keywords: image-guided radiotherapy, cone-beam CT, intra-thoracic anatomical changes, adaptive radiotherapy

MA13.05 NIVOLUMAB IN NON-SMALL CELL LUNG CANCER (NSCLC): THE REAL-LIFE DATA
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Background: Nivolumab has been recently approved by the FDA as a 2nd-line treatment of NSCLC. The data regarding its efficacy in the real-life setting is lacking. Methods: 260 consecutive patients with advanced NSCLC treated with nivolumab at five cancer centers in Israel between January 2015 and March 2016 were observed for OS and toxicity. OS was analyzed by the Cox proportional-hazards regression model. Results: Patient baseline characteristics: median age 67y (range 41-99); males 68%; smokers 76%; ECOG PS ≥2 46%; Non-sq/Sq/other 70%/23%/7%; KRASm/EGFRm/ALK+/other genetic aberration/none/NA 7%/5%/0%/4%/42%/4%; brain metastases 21%; liver metastases 21%; treatment (Tx) line: 1st/2nd/3rd+-line/NA 6%/64%/26%/4%. Median duration of follow-up was 4.3 mo (range 0.1-13.8); median Tx duration was 2.7 mo (range 0.1-15.5); median number of Tx cycles delivered was 6 (range 1-26). 130 (50%) patients died; median OS comprised 6.6 mo (95%CI 5.6-8.6). In univariate and multivariate analysis, the only variable which significantly correlated with OS was ECOG PS (table 1). Median OS of patients with ECOG PS 0/1 and ECOG PS ≥2 comprised 8.6 mo and 3.5 mo, respectively. Safety data is presented in table 2.

(See Table next page)
Table 1. OS analyzes of toxicity with proportional-hazards regression model (multivariable analysis). Abbreviations: SQ = squamous cell carcinoma; NS = non-squamous cell carcinoma; Tx = treatment.

Table 2. Treatment-related adverse events (AE, CTCAE v4.0) reported in ≥23% of patients.

Conclusion: Nivolumab has reasonable efficacy and good safety profile in the real-life setting. ECOG PS ≥2 is associated with poor prognosis.

Keywords: Nivolumab, Anti-PD-1, ECOS PS, non-small cell lung cancer

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MA13.06 INTEGRATIVE GENOMIC PROFILING IDENTIFIES BRAF MUTATIONS AS NOVEL RADIOTHERAPEUTIC TARGETS IN ADENOCARCINOMAS OF THE LUNG

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Background: Patients with non-small cell lung cancer (NSCLC) display a wide spectrum of oncologic outcomes, suggesting significant underlying biologic diversity. However, current radiotherapeutic management is largely homogeneous for a given stage. To advance genotype-directed radiotherapy in NSCLC, we sought to identify genetic determinants of radiosensitivity by leveraging cancer genomic data with a recently developed high-throughput platform for measuring radiation survival. Methods: We used our recently validated high-throughput proliferation assay to profile 104 lung cancer cell lines, including 89 NSCLC and 15 small cell lung cancer (SCLC) lines, for radiation survival. Survival curve analyses permitted quantitative assessment of radiosensitivity. Genomic correlates of radiosensitivity were explored by calculating the information-based similarity metric and correlating genomic parameters by accessing Oncomap data from the Cancer Cell Line Encyclopedia, the COSMIC database of the Cancer Genome Project, and The Cancer Genome Atlas. Results: Radiation survival across cell lines reflected clinical experience regarding differential response to radiation inasmuch as lung squamous cell carcinoma and adenocarcinoma (ACA) had similar radiosensitivity, whereas SCLC and carcinoid were, respectively, more and less radiosensitive. Importantly, radiosensitivity varied more within a lineage than across lineages, with a 6-fold difference in integral survival among ACA lines. Correlation with cancer genomic data revealed BRAF mutations within the most resistant ACA lines (P = 0.0097, FDR = 0.957). A majority of the mutations identified by our analysis have been previously annotated by The Cancer Genome Atlas lung ACA dataset and all hypermorphic mutations identified were located in the highly conserved kinase domain. The majority of mutations have been known to enhance kinase activity in melanoma in a fashion analogous to the well-known BRAF V600E mutation. In line with these findings, we showed that kinase domain mutations were hypermorphic as measured by MEK and ERK1/2 phosphorylation. We also showed that exposure of wild type BRAF cells to radiation results only in a transient activation of MEK and ERK1/2. The MEK inhibitor selumetinib selectively decreased the growth of cells with kinase domain BRAF mutations and sensitized these cells to radiation. Conclusion: BRAF mutations are associated with radiation resistance in lung ACA. Our data nominate MEK inhibitors, a drug class currently in clinical use, as a targeted therapeutic in select BRAF-mutant lung ACA. Further investigation has the potential to yield an additional genotype-directed therapy that could impact up to 4-6% of patients with lung ACA, a frequency comparable to that of ALK rearrangements (4%) or EGFR mutations (10%).

Keywords: MEK inhibitors, precision medicine, radiogenomics, BRAF

MA13.07 TUMOR-TARGETED RADIATION PROMOTES ABDOSCOPAL EFFICACY OF REGIONALLY ADMINISTERED CAR T CELLS: A RATIONALE FOR CLINICAL TRIAL

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Background: Our laboratory has demonstrated the augmented anti-tumor efficacy of intrapleurally administered cancer-antigen mesothelin (MSLN)-targeted chimeric antigen receptor (CAR) T cells (Sci Transl Med 2014), and translated the approach to a clinical trial (NCT02441269) for thoracic malignancies. We hypothesized that regionally administered MSLN CAR T cells can circulate systemically to achieve abscopal anti-tumor efficacy in an antigen-specific manner, and the abscopal efficacy can further be promoted by tumor-targeted radiation therapy (RT). Methods: Using optimized protocols that would permit non-necrotic, well-vascularized tumor growth in pleura, chest wall, peritoneum and flank, tumors were established in immunodeficient (NOD/SCID gamma) mice using mesothelioma or lung adenocarcinoma (LAC) cells. Tumor burden progression, MSLN-targeted CAR T-cell accumulation at primary and distant tumors was monitored by noninvasive bioluminescence imaging (BLI) and tumor volume measurements. Results: A single dose of MSLN CAR T cells administered intrapleurally proliferated (Figure 1A left panel), circulated extrapleurally and accumulated at abscopal sites, including the lymph nodes, chest wall, peritoneum, and flank within 3-5 days, with subsequent T-cell proliferation at abscopal sites (Figure 1A right panel). Primary tumor-targeted, single-dose, thoracic RT prior to T-cell administration augmented T-cell accumulation as demonstrated by BLI (Figure 1B) and tumor-cell quantification (p<0.01). In a mouse model of primary pleural, abscopal antigen-expressing and non-expressing flank tumors (Figure 1C), a single, low-dose, non-cytotoxic thoracic RT enhanced abscopal site CAR T-cell accumulation that resulted in tumor regression (p<0.01; Figure 1D).

Conclusion: Regionally administered mesothelin-targeted CAR T cells proliferate and eradicate the primary tumor, accumulate and demonstrate
anti-tumor efficacy at abscopal sites prior to eradication of the primary tumor in an antigen-specific manner. A single low-dose primary tumor-targeted radiation therapy promotes scopal and abscopal anti-tumor efficacy. These results provide rationale to initiate a clinical trial of combination regional therapies with radiation therapy and CART T cells.

Keywords: CART T-cell immunotherapy, Abscopal Effect, Radiation-Induced Immunomodulation, radiation therapy

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MA13.09 SERIAL FDG AND FLT PET/CT DURING CURATIVE-INTENT CHEMO-RADIOTHERAPY FOR NSCLC IMPACTS PATIENT MANAGEMENT AND MAY PREDICT CLINICAL OUTCOMES
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Background: FDG-PET/CT is the gold-standard for non-small cell lung cancer (NSCLC) diagnosis, staging and tumour delineation prior to chemoradiation therapy (CRT). FDG PET is superior to CT for subsequent response assessment. Sequential interim metabolic and proliferative tumour response assessment with FDG and 3'-Fluorothymidine (FLT) respectively, prior to and during CRT is novel and may predict outcome. Methods: Patients with FDG-PET-Stage I-III NSCLC who were prescribed radical chemo-RT (60 Gy in 30 fractions @ 2/Gwk) were enrolled. FDG and FLT PET/CT scans were performed at baseline and at weeks 2 and 4 of CRT. Intra-treatment tumour response judged by reduction in FDG and FLT uptake was categorised as complete response (CR), partial response (PR), stable (SD) or progressive disease (PD) using EORTC criteria. Overall Survival (OS) and Progression Free Survival (PFS) were measured relative to intra-treatment scan dates and plotted using Kaplan-Meier curves.

Univariate Cox regressions were used to calculate associations between 1. SUVmax of baseline FDG and FLT GTV and 2. intra-treatment FDG and FLT SUVmax and patient outcomes (OS and PFS). Results: Sixty patients were recruited between 2009-13; male 62%; median age 66 years, adenocarcinoma (35%) patients. Distant metastasis was detected in 3 patients on FLT BL and during CRT is novel and may predict outcome. 2.02 (0.87, 4.65) vs 20.09 (4, 114), p=0.012 and PFS [1 vs 2.01 (0.92, 4.37) vs 22.41 (3.348), p=0.026] Associations between the baseline response with patient outcomes (OS and PFS). Results: Sixty patients were recruited between 2009-13; male 62%; median age 66 years, adenocarcinoma (42%). Two-year OS and PFS were 0.51 and 0.26 respectively. Of 332 PET/CT recruited between 2009-13; male 62%; median age 66 years, adenocarcinoma (35%) patients. Distant metastasis was detected in 3 patients on FLT BL and during CRT is novel and may predict outcome. 2.02 (0.87, 4.65) vs 20.09 (4, 114), p=0.012 and PFS [1 vs 2.01 (0.92, 4.37) vs 22.41 (3.348), p=0.026] Associations between the baseline response with patient outcomes (OS and PFS).

Conclusion: The possible association between baseline FLT and PFS merits further investigation. FDG-PET/CT is associated with OS and PFS. The possible association between worse clinical outcomes and early suppression of FLT uptake during CRT may be a result of repair of tumour DNA damage. Baseline FLT, FLT wk2 and FDG wk2 was associated with OS and PFS. Of 332 PET/CT recruited between 2009-13; male 62%; median age 66 years, adenocarcinoma (35%) patients. Distant metastasis was detected in 3 patients on FLT BL and during CRT is novel and may predict outcome. 2.02 (0.87, 4.65) vs 20.09 (4, 114), p=0.012 and PFS [1 vs 2.01 (0.92, 4.37) vs 22.41 (3.348), p=0.026] Associations between the baseline response with patient outcomes (OS and PFS).

Keywords: PET/CT, FDG, FLT, NSCLC

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MA13.10 MAGNETIC RESONANCE IMAGING-GUIDED DELIVERY OF LUNG STEREOTACTIC RADIOTherapy USING PATIENT-CONTROLLED VISUAL GUIDANCE
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Background: Treatment-related toxicity is more common following stereotactic ablative radiotherapy (SABR) for central lung tumors, than is the case for peripheral tumors [Tetar et al 2015]. Further reductions in doses to critical central structures are possible using respiration-gated SABR delivery, but insertion of fiducial markers for gating is also associated with toxicity. We describe a novel approach for clinical delivery of breath-hold gated SABR under continuous MRI guidance. Methods: The MRIdian system permits tumor visualization at 4 frames/second during treatment delivery, with radiation beam-holds whenever the target is outside a prespecified gating window. The gating procedure is as follows: a 17 second inspiration breath-hold MR scan is performed for planning before each SABR fraction (resolution 1.6×1.6×3.0 mm). Image registration is performed, and contours adapted when necessary. A 3mm PTV margin is added, and planned dose distribution recalculated for the ‘anatomy of the day’, and reoptimized. A sagittal plane is chosen for tumor tracking and gating, with a planning target margin of 3 mm. The sagittal tracking view from the MRIdian console is projected on a MR-safe monitor (Cambridge Research), and patients can continuously observe the tracking image using a mirror inside the bore. Results: Six patients were treated with MR-guided gated delivery have been performed in 5 cancer patients with 6 central tumors. All MR-based breath-hold PTVs were smaller (mean 19.8 ± 13.3 cc) than a conventional free-breathing, motion-encompassing approach (mean 36.1 ± 21.9 cc). Plans of a single case are shown in Figure 1. Video-assisted visual feedback achieved a breath-hold gating efficiency of 52% (range 27-88%).

Conclusion: For high-risk SABR cases, use of MR-guided, video-assisted breath-hold gated SABR delivery constitutes a novel treatment method, allowing for optimization of mobility- and setup margins, and for improved verification of SABR delivery. Data from additional patients undergoing treatment will be presented.

Keywords: Stage I NSCLC, SABR, central tumors, MRI-guided delivery

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MA13.11 INVESTIGATING THE FEASIBILITY OF ESTABLISHING A PROSPECTIVE COHORT OF LUNG CANCER PATIENTS FOLLOWING RADIOTHERAPY WITH CURATIVE INTENT
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Figure 1. Comparative treatment plans with standard (TV-based) radiotherapy versus a MRI-guided approach with breath-hold for a central tumor in the left upper lobe of a patient with interstitial lung disease. Panel A shows the routine ITV (7.8cc, pink) for a slices plan, to which a 5 mm margin was added to derive a PTV (26cc, red), and panel B the corresponding dose color-wash for an 8 fraction SABR scheme to 60 Gy. Treatment was performed using online MRI guidance during breath-hold on the MRIdian using a GTV (0.8cc, pink, Panel C), to which a 3 mm setup margin was added (PTV=31.4cc, red). Panel D shows the MRIdian dose color-wash, and Panel E the dose-volume histograms for the adjacent aorta for both plans.

Conclusion: For high-risk SABR cases, use of MR-guided, video-assisted breath-hold gated SABR delivery constitutes a novel treatment method, allowing for optimization of mobility- and setup margins, and for improved verification of SABR delivery. Data from additional patients undergoing treatment will be presented.

Keywords: Stage I NSCLC, SABR, central tumors, MRI-guided delivery

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Background: Worldwide lung cancer is the biggest cause of cancer mortality (Cancer Research UK, 2012) and is the UK’s second most commonly diagnosed malignancy (Macmillan Cancer Support, 2013). Early detection and treatment significantly improves five year survival rates but curative treatments can impact on patients’ health and wellbeing. To date little research has conducted to establish the support needs and recovery patterns of health and wellbeing among lung cancer patients treated with curative intent radiotherapy. This limits our ability to identify those most at risk of poorer health and wellbeing outcomes and target services effectively to support patients better. This study assesses the feasibility of collecting patient reported outcomes measures (PROMs) and clinical details to understand recovery after curative intent radiotherapy treatment for lung cancer.

Methods: This mixed methods study used a prospective, longitudinal cohort design. Eligible patients awaiting curative intent radiotherapy were recruited from six UK sites between October 2015 and June 2016. Questionnaires were completed before undergoing radiotherapy and 3 months later. The questionnaires included validated patient reported outcome measures, including quality of life, symptoms, social support, wellbeing and socio-demographic details. Participants’ medical details were collected by healthcare professionals (HCPs) including cancer type, stage, treatment, and comorbid conditions. Study procedures were evaluated in a qualitative process evaluation.

Results: Of 229 eligible patients, 136 consented to the study with 73% uptake of those approached. A further 13 patients provided consent after being invited to participate. The mean age of patients was 72 years; 29% lived alone; 67% were home owner-occupiers and 20% were current smokers. Baseline EORTC-QLQ-C30 results showed a mean global health status score of 56.9, and a mean functional score of 55.4. The mean scores of 48.8 and 45.0. These are in line with expected scores based on reference data. To date, 9 HCPs, 7 patients and 2 stakeholders have been interviewed as part of the process evaluation, study processes and procedures are deemed acceptable to participants.

Conclusion: This study demonstrates it is feasible to recruit a cohort of lung cancer patients prospectively to assess wellbeing and patterns of recovery following radiotherapy. This novel approach to understanding lung cancer patients’ experiences of survival will enhance our ability to target appropriate and timely support to those most at risk of poorer health and wellbeing.

Keywords: quality of life, Feasibility, Radiotherapy

SESSION MA14: IMMUNOTHERAPY IN ADVANCED NSCLC: BIOMARKERS AND COSTS
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MA14.01 UPDATED DATASET ASSESSING TUMOR MUTATION BURDEN (TMB) AS A BIOMARKER FOR RESPONSE TO PD-1/PD-L1 TARGETED THERAPIES IN LUNG CANCER (LC)
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Background: Immune checkpoint inhibitors (ICPIs) nivolumab and pembrolizumab have been FDA-approved in non-small cell lung cancer (NSCLC). Current IHC based diagnostics are challenged by assay and slide scoring issues and may result in suboptimal treatment allocation, and more robust and comprehensive biomarkers of ICPI efficacy are needed. A discovery set of 64 NSCLCs treated with ICPIs suggested that high TMB (>35 mutations/Mb) significantly correlated with longer time on drug (Spigel et al., ASCO 2016, Abstract 9017). Methods: Comprehensive genomic profiling (CGP) was performed during the course of clinical care. TMB was assessed as the number of somatic, coding, base substitution and indels per Mb of genome. Microsatellite instability-high (MSI-H) or stable (MSI) status was determined using a proprietary algorithm. Results: 15,529 LCCs: 66% adenocarcinoma, 1% sarcomatoid, 14% NSCLC NOS, 11% squamous, 5% small cell, and 2% large cell were assessed. TMB was similar across all lung histologies (median: 6.3, 8.1, 9.0, 9.3, 9.9, and 10.8; the median was 7.6 for all LC cases (TMB >35 in 24% of cases), compared to 4.5 for 80,000+ samples of diverse tumor types in the database. Of Lcs assessed 0.3% were MSI-H, of which 30/31 were TMB-high; however, 24% of MSS-stable cases were also TMB-high. PD-L1 amplification and DNA repair pathway mutation (MLH1, MSH2, POLE) were found in 10.0% and 1.1% of LC cases analyzed, respectively. Tumors harboring known drivers (ALK, ROS1, EGFR, BRAF, V600E, MET splice) had low TMB (median: 2.5, 3.6, 3.8, 3.8, 4.5), whereas tumors with KRAS mutation, non-V600E BRAF mutation, PD-L1 amplification, or DNA repair alterations were more likely to have high TMB (P<0.0001). Conclusion: High TMB may be a predictive biomarker of response to ICPIs. Several factors including lack of a known driver, MSI-H status, PD-L1 amplification, and DNA repair mutation correlated with high TMB (P<0.0001 for all cases). However, 95% of TMB-high cases assessed were MSS and lacked both PD-L1 amplification and DNA repair mutation, and thus would likely not be selected for immunotherapy by assessment of individual genetic alterations or MSI status alone. A validation cohort of NSCLC patients treated with anti-PD-1/PD-L1 therapies including analysis of clinical outcome, TMB, genomic profile, and available clinicopathologic characteristics will be presented. CGP of LCs simultaneously determine TMB, MSI status and PD-L1 amplification, and the presence of driver alterations may provide clinically useful predictors of response to ICPI and other targeted therapies using a single platform, but prospective clinical trials are needed to confirm these observations.

Keywords: NSCLC, tumor mutational burden, comprehensive genomic profiling

MA14.02 EVALUATION OF PD1/PDL1 EXPRESSION ON PERIPHERAL BLOOD CELLS SUBPOPULATIONS IN PATIENTS WITH NON-SMALL CELL LUNG CANCER
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Background: Currently the immune system is considered an important target of study within the therapeutic alternatives for many tumors that have developed resistance in lung cancer. Many molecules called checkpoints regulate antitumor immunity as PD-L1 is expressed in tumour cells and is a biomarker for anti-PD-1/PD-L1 therapy. The expression of PD-L1 in tumour cells or PD-L1 expression in peripheral blood of patients with non-small cell lung cancer has not been widely studied. Methods: We investigated the expression of PD-L1 and its ligands PD-L1 and PD-L2, the antitumor immune response leading to a durable tumor regression. However, the expression of PD-L1/PD-L1 in patients with peripheral blood of patients with non-small cell lung cancer has not been widely studied. Results: We found that 50% of patients with peripheral blood of patients with non-small cell lung cancer were studied and the median expression of PD-L1 was significantly higher than in controls (P<0.001) and the Mean Fluorescence Intensity (MFI) was higher in patients compared to the control group (P<0.001). The expression of PD-L1 in T-helper or CD4+ of NSCLC patients was significantly higher than in cells from control subjects (P<0.001). Similarly, the expression of PD-1 in T cytotoxic cells or CD8+ patients was significantly higher than in controls (P<0.001). In the clinical analysis, we found that a higher percentage of PD-1+ CD3+ cells was statistically associated with tobacco exposure (P=0.0160), and de MFI was associated with the non-adenocarcinoma histology (P=0.0011) additionally, the presence of 3 or more metastases was associated to a higher MFI of PD-1 in CD3+ CD8+ (P=0.0490). In the overall survival (OS) analysis the percentage of CD3+ CD8+ positively correlated with OS (P=0.045). Conclusion: Several studies demonstrate the importance of infiltrating PD-1+ T cells within tumors; however these results showed that the PD-1/PD-L1/PD-L2 expression in peripheral blood cells could be used also as a potential biomarkers in NSCLC patients.

Keywords: PD-1, PD-L1, NSCLC, biomarker

MA14.03 THE IMPACT OF GENOMIC LANDSCAPE OF EGFR MUTANT NSCLC ON RESPONSE TO TARGETED AND IMMUNE THERAPY
TUESDAY, DECEMBER 6, 2016 - 16:00-17:30

MA14. IMMUNOTHERAPY IN ADVANCED NSCLC: BIOMARKERS AND COSTS
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Background: EGFR mutations define a distinct subset of NSCLC characterized by clinical benefit from tyrosine kinase inhibitors. The impact of genomic alterations that coexist with EGFR mutations is not fully understood. In this report, we comprehensively describe the concurrent genomic aberrations in EGFR mutant NSCLC patients and their impact on clinical outcomes. We used rank and Fisher’s exact tests to identify associations between co-concurrent mutations and clinical outcomes. Results: 1985 non-squamous NSCLC patients were identified in the GEMINI database. The frequency of EGFR mutations was 14.4% (n=276). Among EGFR mutant patients, 152 underwent targeted sequencing of a minimum of 66 cancer-related genes. The majority of EGFR mutant patients (77.6%, n=146) had at least one coexisting mutation. The most frequent co-mutations identified were TP53 (47%, n=88), CTNNB1 (7.5%, n=14) and PIK3CA (6.5%, n=12). ALK and ROS1 translocations were found to coexist with EGFR mutations in one patient each. Of 17 patients with a first or second generation TKI, concurrent TP53 mutations were associated with a shorter progression free survival (HR=1.81, P=0.039). Eight patients with EGFR/CTNNB1 co-mutations developed acquired TKI resistance with T790M secondary mutation being the resistance mechanism in six (75%) of them suggesting that coexisting mutation can dictate emerging resistance mechanisms. Ten patients were treated with anti PD/PD-L1 agents (nivolumab n=18, pembrolizumab n=2). Only two (10%) patients achieved confirmed radiological response, one lasting for 6 months and the second ongoing at 6 months. Both patients were never smokers, one with an EGFR L858R mutation and no concurrent mutations, and the other with EGFR exon 19 deletion and TP53 mutation. Sixteen patients developed confirmed progressive disease. Finally, one patient with 17 pack-year smoking history, EGFR G719/S768I double mutation and concurrent PIK3CA mutation achieved stable disease lasting for four months. The median progression free survival for patients treated with immunotherapy was 2 months (1-12 months). Conclusion: Concurrent genomic aberrations may predict response duration to TKIs and may be associated with particular emerging resistance mechanisms to TKIs in EGFR mutant NSCLC. Immunochemistry results in durable clinical benefit in a subset of EGFR mutant NSCLC patients.

Keywords: Targeted therapy, Immunotherapy, EGFR mutant NSCLC

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MA14.05 IMPLICATIONS OF IMPLEMENTATION OF A PD-L1 BIOMARKER-BASED STRATEGY FOR TREATMENT OF ADVANCED NSCLC
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Background: The KEYNOTE-010 (KN010) clinical trial, a multi-center, worldwide, randomized Phase II/III trial of pembrolizumab 2mg/kg every 3 weeks and docetaxel 75mg/m2 every 3 weeks in patients with previously treated advanced NSCLC with PD-L1 positive tumors showed a significant overall survival (OS) advantage for patients receiving pembrolizumab. We examined the improvement in prognoses for patients who elect to receive their PD-L1 biomarker results using extrapolative survival modeling. Methods: Partitioned survival models to project long-term outcomes were developed using data from patients enrolled in KN010, with treated patients in the pembrolizumab 2mg/kg and docetaxel 75mg/m2 arms included in these analyses. As OS for docetaxel patients is not dependent on PD-L1 status, KN010 results were assumed to represent docetaxel efficacy in all patients irrespective of PD-L1 status. The model projected expected lifetime using Kaplan Meier estimates of PFS and OS from KN010 with extrapolation based on parametric functions and long term registry data. Results: Results directly from KN010 showed for patients with TPS≤50%, median survival to be 8.2 months (6.4, 10.7) and 14.9 months (10.4, NA) for docetaxel and pembrolizumab, respectively (HR=0.54 (0.38, 0.77)). Model-based projections show that should all patients be treated with docetaxel, expected median lifetime is 1.0 years. For patients receiving PD-L1 biomarker test per KN010 28.5% would be identified as PD-L1 strong positive (TPS≥50%). PD-L1 (TPS≥50%) predicts a life expectancy with biomarker directed pembrolizumab of 2.25 years on average. Conclusion: Use of PD-L1 biomarker identification can significantly improve OS prognoses for patients considering pembrolizumab and docetaxel with advanced NSCLC based on both clinical trial results and model-based projections from KN010.

Keywords: PD-L1

MA14:06 NIVOLUMAB IN NEVER SMOKER PATIENTS WITH ADVANCED SQUAMOUS NSCLC: RESULTS FROM THE ITALIAN EXPANDED ACCESS PROGRAMME (EAP)
Giuseppe Lo Russo1, Lucio Crinó,2 Domenico Galetta1, Andrea Ardizzoni2, Enrico Cortesi3, Frederico Cappuzzo4, Paola Bordi5, Luana Calabró2, Fausto Barbieri6, Antonio Santo2, Giuseppe Altitavola1, Giacomo Ceranti1, Enrico Mini2, Enrico Vasile1, Flaviana Morgillo4, Alessandro Scoppola4, Carmelo Bengal4, Gianpietro Fasola5, Enrico Ferris6, Francesco Piantedosi6,7
1Fondazione IRCCS - Istituto Nazionale Dei Tumori, Milano/Italy, 2Division of Medical Oncology, Santa Maria della Misericordia Hospital, Perugia/Italy, 3National Cancer Research Centre, Istituto Tumori “Giovanni Paolo II” Bari, Italy, 4Bari/Medical Oncology, S. Orsola-Malpighi University Hospital, Bologna/Italy, 5Sapienza University, Rome/Italy, 6Ausi Romagna, Ospedale Santa Maria Delle Croci, Department of Oncology and Hematology, Ravenna/Italy, 7Medical Oncology Unit, University of Parma, Parma/Italy, 8Medical Oncology and Immunotherapy, University Hospital of Siena, Siena/Italy, 9University Hospital Policlinico di Modena, Oncology Unit, Modena/Italy, 10Gropu (Gruppo Interdisciplinare Veronese Oncologico Piazzon), Azienda Ospedaliera Poliambulanza, Verona, Verona/Italy, 11Department of Hematology and Medical Oncology, University of Messina, Messina/Italy, 12Division of Medical Oncology, A. Cardarelli General Hospital, Napoli/Italy, 13University of Florence, Department of Experimental and Clinical Medicine, Florence/Italy, 14Azienda Ospedaliero Universitaria Pisana Istituto Toscana Tumori, Pisa/Italy, 15Oncologia, Dipartimento Di Istituzional Clinica E Sperimentale “L. Magrassi E A. Lanzara”, Seconda Università Degli Studi Di Napoli, Napoli/Italy, 16Divisione Di Oncologia, I-I-IRCCS, Roma/Italy, 17Division of Medical Oncology, Misericordia Medical General Hospital, Grosseto/Italy, 18Department of Medical Oncology, University Hospital Santa Maria delle Grazie, Udine/Italy, 19Oncologia Medica Azi.A, Olbia/Italy, 20Department of Medical Surgical Oncology and Tharcic Disease, Napoli/Italy

Background: Nivolumab is the first checkpoint inhibitor approved for the treatment of Sq-NSCLC to show a survival benefit vs the standard of care docetaxel in the randomised, phase III, CheckMate 017 study. In the nivolumab development program, a greater clinical benefit was shown in current and former smokers than in never smokers. Never smokers data are available in this respect from a real world setting. For this reason, we decided to use the data collected in the EAP in order to assess the effectiveness and tolerability of nivolumab treatment in the never smoker patient population. Methods: Nivolumab was provided upon physician request for patients aged ≥18 years who had relapsed after a minimum of one prior systemic treatment or for stage IIIIB/IV Sq-NCLCS in the real life. Nivolumab 3 mg/kg was administered intravenously every 2 weeks for ≥24 months. Patients included in the analysis had received ≥1 dose of nivolumab and were monitored for adverse events using Common Terminology Criteria for Adverse Events. Results: Of 372 patients with Sq-NSCLC participating in the EAP in Italy, 38 (10.2%) were never smokers, a proportion very similar to the one observed in Checkmate 017 (10%). With a median number of doses of 8 (range, 1–22) and a median follow-up of 5.6 months, the disease control rate in this group was 50%, including 9 patients with a partial response and 10 with stable disease. Eight patients were treated before RECIST-defined progression, with a 4 of them achieving partial response as a result of their objective response. As of April 2016, median progression-free survival and overall survival were 3.5 months and not reached, respectively. 17 patients (44.7%) discontinued treatment for any reason except toxicity and 5 (13.1%) discontinued due to AE. Conclusion: These preliminary results, although obtained from a small sample size, suggest that nivolumab is effective and well tolerated in a never smoker group of patients with advanced Sq-NLCLS in the real life and warrant further investigation in this area.

Keywords: nivolumab, Squamous NSCLC, never smokers

MA14:07 REAL LIFE EXPERIENCE WITH IMMUNOTHERAPY IN THE...
Netherlands

Robert Schouten, Paul Baas, Michael Van Den Heuvel
Thoracic Oncology, Netherlands Cancer Institute / Antoni Van Leeuwenhoek, Amsterdam/Netherlands

Background: Randomized phase III trials have shown that the PD-1 blocking monoclonal antibody Nivolumab is effective in advanced NSCLC. Nivolumab is registered by the FDA and EMA for treatment of NSCLC. However, approval in The Netherlands was put on hold because of Nivolumab’s high price per quality adjusted life year (QALY). From August 2015, Nivolumab was provided through a compassionate use program. Here we present our experience in treating NSCLC patients with Nivolumab in real life. Methods: Efficacy and safety of Nivolumab was assessed in patients with advanced NSCLC, previously treated with at least one line of platinum-based chemotherapy and an EGFR-PS of ≥2. Nivolumab was administered 2-weekly at a dose of 3 mg/kg intravenously. Response evaluation took place according to RECIST 1.1 at 12 and 24 weeks after start of treatment. Results: In the 10-month period in a single center 189 patients started treatment with Nivolumab, with a mean follow up time of 106 days after start of treatment. Mean age was 62 years (range 29–87), 53% male, 18.5% never smoked, 68% had adenocarcinoma, 20% had squamous histology and 12% were other, mixed or unspecified types.

<table>
<thead>
<tr>
<th>Progressive Disease</th>
<th>12 weeks</th>
<th>24 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease development</td>
<td>65%</td>
<td>80%</td>
</tr>
<tr>
<td>% of total pseudoresponse/progression</td>
<td>PD -&gt; PR</td>
<td>1.90 %</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stable Disease</th>
<th>12 weeks</th>
<th>24 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease development</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% of SD at 12 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SO -&gt; PD</td>
<td>42%</td>
<td></td>
</tr>
<tr>
<td>SO -&gt; SO</td>
<td>40%</td>
<td></td>
</tr>
<tr>
<td>SO -&gt; PR</td>
<td>15%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Partial Response</th>
<th>12 weeks</th>
<th>24 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease development</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% of PR at 12 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>rapid resistance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PR -&gt; PD</td>
<td>11%</td>
<td></td>
</tr>
</tbody>
</table>

Twenty-four percent of patients experience immunotherapy related toxicity, most toxicities were short-term or easily manageable. No grade 5 toxicities, one grade 4 hepatitis and one grade 3 hypophysitis were observed. Hypothyroidism was most frequently observed (gr.1-2; 9.5%), followed by skin-reactions (gr.1-3; 3.8%) and colitis (gr.1-2; 3.2%). Other immune related toxicities were hepatitis (gr.1-4; 2.5%), infusion reactions (gr.1-2; 2.5%), pneumonitis (gr.1-2; 1.9%), hyperthyroidism (gr.1-2; 4.0%) and diabetes mellitus type 1 (gr.1-2; 0.6%). Conclusion: Although follow up is short and response data not yet mature, real-life efficacy and safety data from Nivolumab are comparable to phase III trial data.

Keywords: Immunotherapy, Safety, efficacy, NSCLC

MA14: IMMUNOTHERAPY IN ADVANCED NSCLC: BIOMARKERS AND COSTS
TUESDAY, DECEMBER 6, 2016 - 16:00-17:30

MA14.09 DEMONSTRATING LIFE EXPECTANCY GAINS WITH IMMUNO-ONCOLOGY (IO) THERAPIES
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1Precision Health Economics, Los Angeles/CA/United States of America, 2Bristol-Myers Squibb, Princeton/NJ/United States of America, 3Center for Observational and Real-World Evidence, Merck & Co., Inc, North Wales/PA/United States of America

Background: Immuno-oncology (IO) therapies offer the possibility of long-term survival to metastatic cancer patients. Prior analyses have shown that lung cancer reduces life expectancy by an average of 11.8 years (Burnet NG, et al. Br J Cancer. 2005;92:241-245.). We aimed to investigate the impact of IO therapies on life extension of patients with non-small cell lung cancer (NSCLC). Methods: We used The Health Economics Medical Innovation Simulation (THEMIS) alongside available clinical trial data to estimate the anticipated increase in NSCLC patient survival post-diagnosis resulting from the introduction of IO therapy. THEMIS is an established microsimulation with a 50-year time horizon that tracks a representative sample of patients aged ≥51 years to project longevity. These outcomes were estimated for metastatic NSCLC patients under a pre-IO scenario and compared to a post-IO scenario where IO is available for either first- or second-line treatment. Results: Analysis was classified as either heavy, medium, or light responders, corresponding to reductions in mortality hazards of 96.5%, 64.4%, and 0%, respectively, based on extrapolations of clinical trial results for nivolumab (see table). Health state transitions probabilities and medical expenditures were estimated from nationally representative datasets. Mortality and disease stage were estimated using the Surveillance and Epidemiology End Results (SEER) database. Results: In the pre-IO simulation, metastatic NSCLC patients lose 11.3 years of life (compared with the published 11.8 years). The results from the post-IO scenarios are shown in the table. For comparison, SEER data suggest that survival in metastatic NSCLC patients has only increased by 0.3 years since 1998.

<table>
<thead>
<tr>
<th>Population</th>
<th>Heavy</th>
<th>Medium</th>
<th>Light</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responders</td>
<td>Prevalence</td>
<td>Responders</td>
<td>Prevalence</td>
</tr>
<tr>
<td>Heavy</td>
<td>96.5%</td>
<td>64.4%</td>
<td>0%</td>
</tr>
<tr>
<td>Medium</td>
<td>60%</td>
<td>30%</td>
<td>0%</td>
</tr>
<tr>
<td>Light</td>
<td>100%</td>
<td>0%</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Conclusion: Current IO therapies represent a significant step towards extending life expectancy for metastatic NSCLC patients.

Keywords: immuno-oncology, non-small cell lung cancer, survival, Life expectancy

MA14.10 RELATIVE IMPACT OF DISEASE MANAGEMENT COSTS IN THE ECONOMICS OF PEMBROLIZUMAB IN PREVIOUSLY TREATED PD-L1 POSITIVE ADVANCED NSCLC
Min Huang1, Yanyan Lou1, James Pellissier1, Thomas Burke2, Frank Liu1, Vamsidhar Velcheti1
1Center for Observational and Real-World Evidence, Merck & Co., Inc, North Wales/PA/United States of America, 2Hematology/Oncology, Mayo Jacksonville/FL/United States of America

Background: This study aimed to understand the impact on disease management costs beyond drug acquisition costs in the context of an economic evaluation of pembrolizumab compared with docetaxel in patients in patients with previously treated PD-L1 positive (TPS ≥50%) advanced NSCLC. The analysis was conducted from a US third-party payer perspective. Methods: A partitioned-survival model was developed using data from patients in the KEYNOTE-010 (KN010) clinical trial. The model used KM estimates of PFS and OS from the trial for patients treated with pembrolizumab a mean survival time of 2.1 years. For docetaxel, a mean survival time of 3.25 years was estimated.
Weekly disease management costs observed in KN010 for the progression-free state were $866 and $1,298 for pembrolizumab and docetaxel, respectively. Weekly disease management costs for the progressive disease state were $1,593 based on a US healthcare claim database. Results projected total disease management costs to be $166K per patient treated with pembrolizumab compared with $93K for docetaxel because of extended progression-free and post-progression survival with pembrolizumab. Nearly half (45%) of total expected cost differences between pembrolizumab and docetaxel are due to the incremental disease management costs. Further analyses that exclude drug treatment costs show that the additional disease management costs associated with extended progression-free and overall survival exceed $50,000 per LY gained ($51,864).

Conclusion: Pembrolizumab improves outcomes compared to docetaxel in PD-L1 positive (TPS >50%) pre-treated advanced NSCLC patients in the US. The improved overall survival with pembrolizumab is accompanied by the economic reality of additional non-pembrolizumab costs that represent their own substantial economic burden.

Keywords: Cost-effectiveness, PD-L1, advanced NSCLC

MA14.11 AN ESTIMATE OF THE ECONOMIC IMPACT OF IMMUNOTHERAPY RELATIVE TO PD-L1 EXPRESSION IN BRAZIL - AN UPDATE WITH BRAZILIAN COSTS

Pedro Aguiar Jr1, Ramon De Mello2, Hakaru Tadokoro1, Hans Babiker2, Gilberto Lopes4
1Universidade Federal de SÃo Paulo, SÃo Paulo/Brazil, 2Universidade Do Algarve, Faro/Portugal, 3HNH Health, Scotland/ScottsdaleAZ/United States of America, 4HCOR Cancer Center, SÃo Paulo/Brazil

Background: Delivering high quality cancer care at an affordable cost is one of the main challenges for health care professionals and policy makers, especially in low- and middle-income countries. The objective of our study is to assess the economic impact of nivolumab and pembrolizumab with and without the use of PD-L1 as a biomarker in Brazil. Methods: We developed a decision-analytic model to determine the cost-effectiveness of PD-L1 assessment and the second-line treatment with NIVO or PEMBRO versus docetaxel. The model used outcomes data from randomized clinical trials and drug acquisition costs were estimated using current prices in Brazil. Thereafter, we used Brazilian epidemiologic data to estimate the economic impact. Results: We included three RCTs (two with NIVO and one with PEMBRO). The estimated number of cases eligible for therapy with immune checkpoint inhibitors is 4,733. Treating all patients with NIVOLUMAB would cost $117 million dollars each year, representing an increase of 21% in current Brazilian expenses for cancer drugs acquisition. Treating only patients with PD-L1 >1% with NIVOLUMAB would cost 93 million dollars every year, leading to an increase of 11.3% in expenses for cancer drugs acquisition. However, with such selection, up to 46% of cases would not be treated and 315 years of life would be lost compared to treating all patients regardless of PD-L1 expression. The cost of each year of life saved was improved by PD-L1 selection (from US$ 196,000 to US$ 164,000). Table 1 summarizes our findings for five different scenarios of treatment. The results were similar with NIVOLUMAB and PEMBROLIZUMAB.

<table>
<thead>
<tr>
<th>SCENARIO</th>
<th>QALY GAIN ICER (US$)</th>
<th>LIFE-YEARS SAVED</th>
<th>YEARS OF LIFE NOT SAVED</th>
<th>% NOT TREATED</th>
<th>TOTAL COST (US$)</th>
<th>IMPACT ON TOTAL CANCER DRUG EXPENDITURE</th>
<th>COST/LYS (US$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIVO ALL COMERS</td>
<td>0.164 129 K</td>
<td>885</td>
<td>0</td>
<td>0%</td>
<td>173 Million</td>
<td>21.1%</td>
<td>196 K</td>
</tr>
<tr>
<td>NIVO PD-L1 &gt;1%</td>
<td>0.201 108 K</td>
<td>570</td>
<td>315</td>
<td>46%</td>
<td>93</td>
<td>11.3%</td>
<td>164 K</td>
</tr>
<tr>
<td>PEMBRO PD-L1 &gt;1%</td>
<td>0.138 137 K</td>
<td>666</td>
<td>NA</td>
<td>34%</td>
<td>100</td>
<td>12.1%</td>
<td>150 K</td>
</tr>
<tr>
<td>NIVO ALL SQ/ &gt;1% NSQ</td>
<td>0.216 99 K</td>
<td>738</td>
<td>147</td>
<td>35%</td>
<td>116</td>
<td>14.0%</td>
<td>157 K</td>
</tr>
<tr>
<td>PEMBRO PD-L1 &gt;1%</td>
<td>0.164 116 K</td>
<td>285</td>
<td>NA</td>
<td>72%</td>
<td>43</td>
<td>5.2%</td>
<td>151 K</td>
</tr>
</tbody>
</table>

Conclusion: The use of PD-L1 expression as a biomarker for treatment with immune checkpoint inhibitors decreases the overall economic impact and the cost per life-year saved. Further study and societal discussion is needed in order to find the optimal strategy for patient selection.

Keywords: Pharmacoeconomy, Policy Maker, Immunotherapy, biomarker
The expression of genes related to cancer-immunity was assessed and normalized; immunogram was drawn in a radar chart composed of 8 axes reflecting 8 steps of cancer-immunity cycle. Results: Distinctive patterns of immunogram were observed in lung cancer patients: T-cell-rich and T-cell-poor. Patients with T-cell-rich pattern had gene signatures of abundant T-cells, Tregs and MDSCs, checkpoint molecules and immune-inhibitory molecules in the tumor, suggesting the presence of counter regulatory immunosuppressive microenvironment. No release of counter regulations, i.e. checkpoint inhibitors, may be indicated for these patients (Figure A). Immunogram of T-cell-poor phenotype reflected lack of anti-tumor immunity, inadequate DC activation, and insufficient antigen presentation in the tumor (Figure B). When the immunograms were overlaid within each tumor histology, no typical pattern was elucidated. Both T-cell-rich and T-cell-poor phenotypes were present in each histology, suggesting that histology cannot necessarily reflect the cancer-immunity status of the tumor (Figure C,D). These results were consistent with previous studies showing that clinical responses of checkpoint blockade were not easily predicted by the histology.

Conclusion: Utilizing the immunogram, the landscape of the tumor microenvironment in each patient can be appreciated. Immunogram for the cancer-immunity cycle can be used as an integrated biomarker and thus may become a helpful resource toward optimal personalized immunotherapy.

Keywords: cancer-immunity cycle, neoantigen, immunogram, transcriptome

MA15.02 NON-SYNONYMOUS MUTATION BURDEN IN LUNG CARCINOMA IS ASSOCIATED WITH DURABLE CLINICAL RESPONSE TO IMMUNE CHECKPOINT BLOCKADE
Navin Mahadevan¹, Anika Adeni², Peter Hammerman³, Mark Awad⁴, Leena Gandhi⁵, Lynette Sholl¹
¹Pathology, Brigham and Women's Hospital, Boston/United States of America
²Medical Oncology, Dana-Farber Cancer Institute, Boston/MA/United States of America
³Lowe Center for Thoracic Oncology, Dana-Farber Cancer Institute, Boston/MA/United States of America
⁴Pathology, Brigham and Women's Hospital, Boston/MA/United States of America

Background: Recent evidence indicates that efficacy and durability of responses to immune checkpoint inhibitors in lung carcinomas correlate with increased nonsynonymous mutation (NSM) burden, putative neoantigen number, and in some tumor types, PD-L1 protein expression. In this study, we retrospectively analyzed the relationship of lung carcinoma mutation burden, PD-L1 expression and immune infiltrates with clinical response in patients receiving immune checkpoint blockade. Methods: Tumor nonsynonymous mutation data derived from clinical targeted next generation sequencing (309 genes) of lung carcinomas from 94 patients treated with immune checkpoint inhibitors was correlated with clinical outcomes, including durable clinical benefit (DCB; >6 months partial or stable response) and progression-free survival (PFS). PD-L1 immunohistochemistry (clone E1L3N, Cell Signaling Technology, Envision+ detection, Dako) was considered positive if ≥1% of tumor cells and/or tumor-infiltrating immune cells (IC) stained. PL1, CD3, and FOXP3 immunohistochemistry was used to highlight tumor-associated macrophages and non-regulatory and regulatory T-cell populations, which were manually quantified per mm². Results: The mean patient age was 62 years (range: 32-91 years). Lung tumor types included 69 adenocarcinomas, 11 squamous cell carcinomas, 5 small cell carcinomas, and 9 of other/combined histology. Therapies included PD1 inhibitors (82), a PD-L1 inhibitor (5) and multiple agents (7). Across all tumor types, patients with DCB had a significantly higher number of NSM (range: 142-700) compared to patients who showed no durable benefit (NDB; DCR; p = 0.0027). Patients with greater than the median number of NSM (9) had significantly longer PFS than those with ≤9 (p = 0.015). Increasing smoking history correlated with higher mutation load (p = 0.047) and patients with a longer smoking history tended to have longer PFS although this trend did not reach statistical significance (p = 0.07). Expression of PD-L1 in either tumor cells or ICs was not associated with high NSM burden (p = 0.47) or PFS (p = 0.92). PD-L1 expression in the tumor microenvironment was associated with increased numbers of tumor-associated macrophages (p = 0.0002), and non-regulatory and regulatory T-cells (p = 0.0038 and 0.01 respectively). Conclusion: The non-synonymous mutation burden in lung carcinoma as assessed by targeted next generation sequencing is associated with increased PFS and durable clinical benefit to immune checkpoint inhibitors. In this limited cohort, PD-L1 expression using clone E1L3N does not predict response to these therapies. We add to growing evidence that increased somatic mutations in carcinomas influence response to immune checkpoint blockade.

Keywords: Mutation burden, Immunotherapy, next generation sequencing

MA15.03 THE PREDICTIVE VALUE OF MUTATION/NEOANTIGEN BURDEN FROM CTDNA ON THE EFFICACY OF PD-1 BLOCKADE IN ADVANCED NSCLC
Weijing Cai¹, Canen Zhou², Chuxia Su³, Feng Ying Wu⁴, Shengxiang Ren⁵, Xiaoxia Chen⁶, Fred R. Hirsch⁷
¹Medical Oncology, Shanghai Pulmonary Hospital, Shanghai, China
²Division of Medical Oncology, University of Colorado Anschutz Medical Campus, Aurora/CO/ United States of America

Background: Immune checkpoint, PD-1, inhibitors, have been approved to treat advanced NSCLC patients without oncogenic driver in the second-line setting based on durable clinical benefit. It has been demonstrated that the overall mutation burden in tumor tissue is significantly associated with progression free survival (PFS) of advanced NSCLC patients treated with PD-1 inhibitor. However, tumor tissue may not be available from all patients at any time during PD-1 blockade therapy. Therefore, the purpose of this study was to explore the predictive value of mutation/neoantigen burden from ctDNA on efficacy of PD-1 inhibitors. Methods: We treated advanced NSCLC patients without oncogenic drivers with PD-1 inhibitor in the second or more line setting. The whole-exome of tumor tissues and ctDNA at baseline and ctDNA at every time of efficacy evaluation from these patients were sequenced by NGS. The hybrid-capture-enriched libraries were sequenced on the Illumina HiSeq 4000 platform with 75-base paired-end reads, sequencing depth was 300 for ctDNA whole-exome sequencing. We compared the results of whole-exome sequencing between patients who achieved objective response to PD-1 inhibitor and patients who experienced disease progression. Besides, we also compared the results of whole-exome sequencing between baseline ctDNA and ctDNA extracted at efficacy evaluation. Results: Up to now, a total of 23 patients treated with PD-1 inhibitor received efficacy evaluation at least once in this study. Of them, 4 patients achieved partial response (PR), 3 patients achieved stable disease (SD). Of 4 patients with PR, 3 patients were found to harbor high mutation burden (more than 400 nonsynonymous mutations) from ctDNA and only 1 patient harbored mutation burden of less than 100 from ctDNA at baseline. We found the mutation or neoantigen burden from ctDNA changed during PD-1 blockade therapy. The efficacy of PD-1 inhibitor appeared to be more significantly associated with neoantigen burden rather than mutation burden. Only one ctDNA sample was found positive for MSH6 mutation (C1373X) and all baseline ctDNA samples were negative for microsatellite instability (MSI) status. Conclusion: Evaluating nonsynonymous mutation burden/neoantigen burden from ctDNA was feasible in advanced NSCLC patients treated with PD-1 inhibitors. The predictive value of neoantigen burden from ctDNA on the efficacy of PD-1 inhibitor may be better than that of mutation burden in advanced NSCLC. It may not be feasible to determine the status of mismatch-repair deficiency and MSI using ctDNA samples in advanced NSCLC. An expanded study is ongoing. More details will be presented in the conference.

Keywords: neoantigen burden, ctDNA, PD-1 blockade, Mutation burden

MA15.05 PD-L1 IMMUNOHISTOCHEMISTRY AS BIOMARKER IN NON-SMALL CELL LUNG CANCER (NSCLC)
Dagmar Krenbek¹, Barbara Weidinger², Christa Jarius³, Sophia Holzer³, Andrea Mohn-Staudner⁴, Maximilian Hochmair⁵, Andreas Chott⁶, Ulrike Setinek⁷
¹Otto Wagner Hospital, Department of Pathology, Vienna/Austria
²Otto Wagner Hospital, Department of Respiratory and Critical Care Medicine, Vienna/Austria

Evaluating PD-L1 expression by immunohistochemistry (IHC) has become a widely utilized approach for the prediction of immune checkpoint inhibitor benefit. However, the benefit of PD-L1 IHC in NSCLC patients treated with anti-PD-1 inhibitors is still under investigation. We treated advanced NSCLC patients with anti-PD-1 inhibitor. However, tumor tissue may not be available from all patients at any time during PD-1 blockade therapy. Therefore, the purpose of this study was to explore the predictive value of mutation/neoantigen burden from ctDNA on efficacy of PD-1 inhibitors. Methods: We treated advanced NSCLC patients without oncogenic drivers with PD-1 inhibitor in the second or more line setting. The whole-exome of tumor tissues and ctDNA at baseline and ctDNA at every time of efficacy evaluation from these patients were sequenced by NGS. The hybrid-capture-enriched libraries were sequenced on the Illumina HiSeq 4000 platform with 75-base paired-end reads, sequencing depth was 300 for ctDNA whole-exome sequencing. We compared the results of whole-exome sequencing between patients who achieved objective response to PD-1 inhibitor and patients who experienced disease progression. Besides, we also compared the results of whole-exome sequencing between baseline ctDNA and ctDNA extracted at efficacy evaluation. Results: Up to now, a total of 23 patients treated with PD-1 inhibitor received efficacy evaluation at least once in this study. Of them, 4 patients achieved partial response (PR), 3 patients achieved stable disease (SD). Of 4 patients with PR, 3 patients were found to harbor high mutation burden (more than 400 nonsynonymous mutations) from ctDNA and only 1 patient harbored mutation burden of less than 100 from ctDNA at baseline. We found the mutation or neoantigen burden from ctDNA changed during PD-1 blockade therapy. The efficacy of PD-1 inhibitor appeared to be more significantly associated with neoantigen burden rather than mutation burden. Only one ctDNA sample was found positive for MSH6 mutation (C1373X) and all baseline ctDNA samples were negative for microsatellite instability (MSI) status. Conclusion: Evaluating nonsynonymous mutation burden/neoantigen burden from ctDNA was feasible in advanced NSCLC patients treated with PD-1 inhibitors. The predictive value of neoantigen burden from ctDNA on the efficacy of PD-1 inhibitor may be better than that of mutation burden in advanced NSCLC. It may not be feasible to determine the status of mismatch-repair deficiency and MSI using ctDNA samples in advanced NSCLC. An expanded study is ongoing. More details will be presented in the conference.

Keywords: neoantigen burden, ctDNA, PD-1 blockade
Background: Anti-PD1 (programmed cell death 1) therapeutic antibodies have recently become available as a promising option in the treatment of patients with NSCLC in Austria. Several clinical studies suggested PD-L1 (programmed death-ligand 1) protein expression in tumors cells to be a useful prognostic biomarker using several antibodies and different cutoffs. We studied PD-L1 expression in our NSCLC patient cohort and compared the performance of different antibodies. Furthermore we aimed to investigate the value of PD-L1 expression as a biomarker in a subset of patients treated with Anti-PD1 immunotherapy.

Methods: PD-L1 immunohistochemistry (IHC) was performed in 437 lung cancer specimens (316 adenocarcinomas, 77 squamous cell carcinomas and 44 NSCLC NOS) using the clones SP263 (Ventana), 28.8 (Abcam) and E1L3N (Cell Signaling) on the VENTANA IHC platform. The percentages of tumor cells (TC) with membranous staining were determined - irrespective of staining intensity; TC-counts of less than 1% were interpreted as negative. Staining with at least two of the three antibodies was available in 378 specimens (SP263/28.8 in 320 and 28.8/E1L3N in 177). 60 specimens were stained with three antibodies. From 58 patients receiving Nivolumab clinical information about response to therapy was available.

Results: PD-L1 was expressed in 244 specimens (54.8%) 112 (25.6%) showed TC-counts ≥50%, and 132 (30.2%) were <50%, 193 (44.16%) were negative. SP263 showed stronger staining intensity than 28.8 and E1L3N. Differences in TC-percentage were seen in 67 of 378 specimens, with major changes in 16 specimens (negative to positive in 4 and >50% to <50% in 12 cases). Higher TC percentages were seen with SP263. In the 58 treated patients complete remission was seen in 6 (4 ≥50%, 2 negative), partial remission in 14 (10 ≥50%, 3 <50%, 1 negative), stable disease in 4 (2 ≥50%, 2 negative), paradox reaction in 1 (1 ≥50%, 3 <50%, 3 negative) and progressive disease in 27 (4 ≥50%, 16 >50% and 7 <50%). Conclusion: PD-L1 immunoexpression was expressed in the majority of NSCLC patients. Despite minor differences in the expression levels all three tests provided reliable results. Furthermore PD-L1-IHC showed to be a useful biomarker in NSCLC especially concerning the good response to Anti-PD1 therapy in tumors with PD-L1 expression ≥50%. However as some PD-L1 negative tumors also responded, negative test results cannot definitely exclude patients from immunotherapy.

Keywords: non-small cell lung cancer, PD-L1 immunohistochemistry, Immunotherapy

MA15: IMMUNOTHERAPY PREDICTION
WEDNESDAY, DECEMBER 7, 2016 - 14:15-15:45

MA15.07 MOLECULAR DETERMINANTS OF LACK OF TUMOR IMMUNE INFILTRATION IN NSCLC
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Background: Non-small cell lung cancer (NSCLC) make up the majority of all lung cancer cases and is associated with very poor prognosis. Immune checkpoint blockers have now been shown to induce unprecedented durable responses in a fraction of NSCLC patients with programmed cell death ligand (PD-L1) expression within their tumor. However in order to improve their efficiencies beyond this subset of patients, a detailed molecular characterization to identify factors associated with lack of T cell infiltration is needed. A recent analysis in metastatic melanoma identified Wnt/B-catenin pathway activation as a mechanism for lack of T cell infiltration. We pursued similar analyses of immunologic gene signatures and molecular associations in squamous cell lung cancer (SCC) and lung adenocarcinoma (LA). Methods: We analyzed RNAseq data from two lung cancer datasets of The Cancer Genome Atlas (TCGA) (N = 449 for SCC and N = 514 for LA). Samples were categorized into non-T cell inflamed and T cell inflamed groups using unsupervised consensus clustering based on the expression of 160 immune-related genes. Ingenuity pathway analysis was utilized to identify molecular pathways activated in non-T cell-inflamed tumors. Results: A similar proportion of non-T cell-inflamed tumors were identified in the two cohorts (SCC: 34%; LA: 37%). 47% of the SCC tumors were identified as T cell inflamed, as compared to 37% in LA. A positive correlation was observed between CD8A and PD-L1, IDO1, LAG3 and TIM3 (p<0.0001). Total of 1216 genes are significantly up-regulated in non-T cell-inflamed SCC tumors and 596 in LA with at least 1.5-fold change and FDR-adjusted p<0.05. Among these, a total of 194 genes are up-regulated in both SCC and LA, with the rest being specific for each subtype (SCC: 84%; LA: 67%). Pathway analysis suggested 35 upstream regulators were activated in SCC and 32 in LA (activation z-score>2.0). Among these, 10 upstream regulators are activated in both datasets (ATF4, FYNB, KAT6A, KLF4, MYC, NEFL2, PDK1, SCAP, SPTI, SREBF2). Finally, we performed the same gene expression analysis on RNAseq data from matched normal tissues (N = 51 for SCC and N = 59 for LA) and confirmed that the T cell inflamed gene signature is a property of the tumor rather than normal lung tissue. Conclusion: Our analyses successfully identified genes and associated pathways that are enriched in NSCLC subtypes with no immune infiltration. Rational strategies to improve the efficacy of immune checkpoint blockers beyond the current subset of responders should be based on targeting these pathways.

Keywords: biomarker, non-small cell lung cancer, immunotherapy biomarker

MA15: IMMUNOTHERAPY PREDICTION
WEDNESDAY, DECEMBER 7, 2016 - 14:15-15:45

MA15.06 PREDICTIVE VALUE OF MEASURING SOMATIC MUTATIONS AND TUMOR INFILTRATING LYMPHOCYTES FOR PD-1 AXIS THERAPY IN NON-SMALL CELL LUNG CANCER (NSCLC)
Scott Gettinger1, Jungmin Choi1, Nikita Mani1, Ila Datari1, Edward Kafdan1, Sarah Goldberg2, Daniel Zelterman1, Kurt Schalper1, Edward Kaftan1, Richard Lifton2, David Rimm3, Roy Herbst1
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Background: Diverse factors have been associated with clinical benefit to PD-1 axis blockers in NSCLC including PD-L1 protein expression by immunohistochemistry and increased mutation load/predicted class I neoantigens. However, the association and predictive value of the tumor genomic landscape, composition of the tumor immune microenvironment and T-cell function remain unclear. Methods: We performed whole exome DNA sequencing and multiplexed quantitative immunofluorescence (QIF) for T-cells in pre-treatment FFPE samples from 45 NSCLC patients treated with PD-1 axis blockers (alone or in combination) in our institution. Genomic analysis was used to evaluate the mutational load and predicted class-I neoantigens. Multiplexed QIF-based immunoprofiling was used to measure the level of CD8+ Tumor infiltrating lymphocytes (TILs), in situ T-cell proliferation (Ki-67 in CD3+ cells) and T-cell activation (Granzyme-B in CD3+ cells). We studied the association between the tumor somatic mutations, predicted neoantigens, T-cell infiltration/function and clinical benefit/survival. Results: Increased mutational load was positively associated with predicted class-I neoantigens, variable damage repair genes, smoking and absence of activating mutations in EGFR, but not associated with the level of CD3+ T-cells, T-cell proliferation (Ki-67 in CD3+ cells) and function (Granzyme-B in CD3+ cells). Increased mutations and candidate class-I neoantigens were significantly associated with response to therapy (P < 0.02 and 0.03, respectively), but not with overall survival (median cut-point, log rank P = 0.92 and 0.80, respectively). Higher CD3 positivity was not associated with response to therapy (P > 0.17), but was significantly associated with overall survival (median cut-point, log rank P = 0.03). Regardless of the mutational load and candidate neoantigen content, elevated CD3 with low Ki-67/Granzyme-B in CD3 predicted longer survival after PD-1 axis blockade than high CD3/high Ki-67/Granzyme-B in CD3, or low T-lymphocyte infiltration. Conclusion: Increased somatic mutations are associated with smoking and response to PD-1 agents, but not with tumor T-cell infiltration/activation and overall survival. Regardless of the mutational load, increased T-cell infiltration using QIF is significantly associated with longer survival after PD-1 axis blockade in NSCLC. The subgroup of NSCLC with the highest potential of benefit to immune reinvigoration using PD-1 axis blockade comprise tumors with elevated lymphocyte infiltration but low in situ activation/proliferation.

Keywords: Immunogenomics, Immunoprofiling, PD-1 axis blockers, non-small cell lung cancer

MA15: IMMUNOTHERAPY PREDICTION
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MA15.09 RESPONSE TO THE TREATMENT IMMEDIATELY BEFORE NIVOLUMAB MONOTHERAPY MAY PREDICT CLINICAL RESPONSE TO NIVOLUMAB
Haruki Kobayashi1, Shota Omoi1, Kazuhisa Nakashima1, Kazuhige Wakuda2, Akira Ono1, Hirotsugu Kenmotsu1, Tateaki Naito1, Haruyasu Murakami1, Masahiro Endo1, Yoshiaki Takahashi1
1Division of Thoracic Oncology, Shizuoka Cancer Center, Shizuoka/Japan, 2Shizuoka Cancer Center, Shizuoka/Japan

Background: Nivolumab was approved in Japan on December 17, 2015 for previously treated non-small cell lung cancer (NSCLC). The expression of programmed death-ligand 1 (PD-L1) in tumor tissue is considered a predictive factor for clinical response to nivolumab. However, in Japan, there are no commercially available diagnostic kits for evaluating PD-L1 expression. In addition, little is known regarding other predictive factors of response to
nivolumab monotherapy in patients with NSCLC. Therefore, we examined the relationships between the response to nivolumab monotherapy and clinical parameters in patients with NSCLC. Methods: Between December 2015 and April 2016, we performed a retrospective analysis of 50 patients with NSCLC treated with nivolumab monotherapy (3 mg/kg, every 2 weeks) at our Institution in the clinical setting. Results: Baseline characteristics of patients who received nivolumab monotherapy were: median age, 65 years (range:39–76); 60% male; 26% ECOG-PS 0, 64% ECOG-PS 1; 38% smoker; 58% stage IV disease, 22% postoperative recurrence; 80% non-squamous NSCLC, 36% non-SQ NSCLC patients had active EGFR mutations; 20% second-line, 18% third-line. The objective response rate (ORR) for all patients treated with nivolumab monotherapy was 18% (95%CI 10–31). Univariate analysis revealed that predictive factors of response to nivolumab monotherapy were associated with “SQ”, “response to the treatment immediately before nivolumab monotherapy”, “therapeutic line of nivolumab (second-line and third-line treatment)” and “smoker” categories (Table 1). In the multivariate logistic regression analysis, the independent predictive factors were “SQ” (P = 0.0069) and “response to the treatment immediately before nivolumab monotherapy” (P < 0.0001) (Table 1).

Conclusion: This work provides evidence that TP53 and KRAS mutation in lung adenocarcinoma may be served as a pair of potential predictive factors in guiding PD-1 blockade immunotherapy.

Keywords: programmed cell death protein-1 (PD-1) blockade, KRAS, lung adenocarcinoma, Nivolumab.

MAIS: IMMUNOTHERAPY PREDICTION WEDNESDAY, DECEMBER 7, 2016 - 14:15-15:45

MAIS.10 POTENTIAL PREDICTIVE VALUE OF TP53 AND KRAS MUTATION STATUS FOR PD-1 BLOCKADE IMMUNOTHERAPY IN LUNG ADENOCARCINOMA
Zhong-Yi Dong, Wen-Zhao Zhong, Si-Yang Liu, Zhi Xie, Si-Pei Wu, Yi Long Wu
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Background: Although clinical studies have shown promise for targeting programmed cell death protein-1 (PD-1)-ligand (PD-L1) signaling in non-small cell lung cancer (NSCLC), the factors that predict which subtype patients will be responsive to checkpoint blockade remains elusive. This study was sought to identify the potential biomarkers that predicted response to PD-1 blockade immunotherapy in lung adenocarcinoma. Methods: We performed an integrated analysis on the multiple-dimensional data types including genomic, transcriptomic, proteomic and clinical data from cohorts of both lung adenocarcinoma public database including The Cancer Genome Atlas (TCGA), GEO repository (GSE72094) and Broad dataset, and clinical immunotherapeutic patients in our center. Gene Set Enrichment Analysis (GSEA) was used to determine potentially relevant gene expression signatures between specific subgroups. Results: We observed distinct function of TP53 and KRAS mutation in regulating immune tumor microenvironment (TME). It is TP53 mutation but not KRAS mutation in lung adenocarcinoma that significantly increased expression of immune checkpoints, facilitated CBB-T cell infiltration and activated T-effector and interferon-γ (IFN-γ) signature. Interestingly, TP53 and KRAS co-mutated subgroup manifested exclusive increased expression of PD-L1 and a highest proportion of PD-L1+/CD8A+. More importantly, TP53 or KRAS mutated tumors showed prominently increased mutation burden and specifically enriched in the transversion-high (TH) cohort. Further analysis focused on the potential molecular mechanisms revealed that TP53 or KRAS mutation altered a group of genes involved in cell cycle regulating, DNA replication and damage repair. Finally, clinical immunotherapeutic data were further confirmed that TP53 or KRAS mutation lung adenocarcinoma patients, especially those with co-occurring TP53/KRAS mutations, showed remarkable clinical benefit to PD-1 blockade immunotherapy.

Conclusion: “Response to the treatment immediately before nivolumab monotherapy”, other than “SQ” histology may be predictors of clinical response to nivolumab in patients with NSCLC.

Keywords: Nivolumab, a predictive factor, non-small cell lung cancer

MAIS: IMMUNOTHERAPY PREDICTION WEDNESDAY, DECEMBER 7, 2016 - 14:15-15:45

MAIS.11 ACQUIRED RESISTANCE MECHANISMS TO EGFR KINASE INHIBITORS ALTER PD-L1 EXPRESSION STATUS IN LUNG CANCER
Kenichi Suda1, Leslie Rozeboom2, Christopher Riviard3, Hui Yu1, Mary Ann Melnick1, Trusa Hirz1, Kim Ellison1, Daniel Chan1, Karin Peters1, Lynn Heasley1, Tetsuya Mitsudomi2, Fred R. Hirsch1
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Background: Immunotherapies that target PD-1/PD-L1 exploit the primary roles of cytotoxic agents in lung cancers. However, tyrosine kinase inhibitors (TKIs) are still considered to be the first choice in lung cancer patients with EGFR mutations. Although immunotherapies may be applied as second line or later therapeutic approaches in these patients, after acquisition of resistance to EGFR-TKIs, it is unclear if acquired resistance mechanisms alter PD-L1 expression status that is employed as an important predictive biomarker for PD-1/PD-L1 targeting agents. Methods: Lung cancer cell lines with EGFR mutations (HCC827, HCC4006, PC9, and H1975) and their isogenic descendants with acquired resistance to various EGFR-TKIs were examined in this study. The resistance mechanisms of descendants include T790M secondary mutation, MET gene amplification, epithelial to mesenchymal transition (EMT), and loss of amplified EGFR mutant allele. PD-L1 expression status was analyzed by immunohistochemistry (IHC) and immunoblotting. Effects of acquired resistance mechanisms on PD-L1 expression were also evaluated by shRNA mediated knockdown of candidate molecules, and co-localization analysis using fluorescent imaging. IFN-gamma was used to mimic immune cell attack. Published microarray data of cells with acquired resistance to EGFR-TKIs were also employed to evaluate our findings. Results: PD-L1 expression was upregulated in several resistant cells and correlated with EGFR activation. In addition, we found that the phosphorylation of EGFR tyrosine (Y) 992 site, but not Y845, Y1068, or Y1234, was correlated with increased expression of PD-L1. We also observed that TK1-resistant cells with marked E-cadherin downregulation (HCC4006) elortinib resistant cells and H1975 osimertinib resistant cells), one of hallmarks of EMT, showed decreased expression of PD-L1. However, one cell line (853#10), displaying EMT-like phenotype but only slight E-cadherin downregulation, showed PD-L1 upregulation. Published
SESSION MA16: NOVEL STRATEGIES IN TARGETED THERAPY
WEDNESDAY, DECEMBER 7, 2016 - 14:15-15:45

MA16.01 TARGETED GENE THERAPY FOR TOBACCO CARCINOGEN-INDUCED LUNG CANCER
Nomundelger Ganjkhuu,1 Chong-Su Cho2
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2Agricultural Biotechnology and Research Institute for Agriculture and Life Science, Seoul National University, Seoul/Korea, Republic of

Background: Rab25, a member of Rab family of small GTPases, is associated with progression of various types of human cancer including lung cancer that is the leading cause of cancer-associated deaths around the globe. Methods: In this study, we report the gene therapeutic effect of short hairpin Rab25 (shRab25) on 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)-induced lung tumorgenesis in female A/J mice. Initially, Mice (six-week-old) were injected with single dose of NNK (2 mg/0.1 ml saline/mouse) by intraperitoneal injection to induce the tumor. 8 weeks later, shRab25 was delivered with GPT-SPE (glycerol propoxylate triacrylate (GPT) and spermine) complex into both parental and in resistant cells with E-cadherin downregulation, however PD-L1 expression in resistant cells was still lower and localized mainly in the cytoplasm rather than the cell membrane. Conclusion: We observed a dramatic change of PD-L1 expression status in lung cancers with EGFR mutation after acquisition of resistance to EGFR-TKIs, depending on the resistance mechanisms. These results support the importance of re-biopsy after acquisition of resistance to EGFR-TKIs, not only for the resistance mechanisms but also for the evaluation of PD-L1 expression status.

Keywords: EGFR mutation, epithelial to mesenchymal transition, T790M mutation, EGFR-TKIs

MA16.02 MUTATIONAL LANDSCAPE OF TKI NAIVE AND RESISTANT EGFR MUTANT LUNG ADENOCARCINOMAS
Katherine Hastings1, Jungmin Choi1, Anna Wurtz2, Zenta Walther1, Guoping Cai1, Isabel Oliva3, Ziming Zhao4, Stephen Gaffney5, Atila Lamarino6, Siming Zhao7, Mark Bi8, Sarah Goldberg1, Anne Chung9, Zongzhi Liu10, Jeffrey Townsend11, Joseph Schlessinger12, Richard Lifton13, Roy Herbst14, Scott Gettinger15, Katerina Politi16
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Background: The identification and development of tyrosine kinase inhibitors (TKIs) targeting the epidermal growth factor receptor (EGFR) have revolutionized and greatly improved the treatment of EGFR-mutant non-small cell lung cancer (NSCLC). Unfortunately, acquired resistance (AR) to these agents remains a major clinical problem hindering durable responses. Although significant work has been done to identify particular mechanisms of acquired resistance, little is known regarding the global mutational landscape of EGFR mutant tumors before therapy or at the manifestation of acquired resistance. Methods: Using specimens obtained in the IRB approved, Yale Lung Rebiopsy program, we completed whole exome sequencing of 15 EGFR mutant tumors with paired tissue obtained pre-treatment and at the time of AR to EGFR TKIs. An additional 5 unpaired AR samples were also analyzed. The mutational burden and copy number profile of the specimens were studied. Results: We found that the mutational burden of pre-treatment EGFR mutant tumors varies widely between tumors. TKI treatment, however, does not significantly alter the overall or non-synonymous mutation load at AR. Interestingly, EGFR mutant tumors had a significantly higher mutation burden at acquired resistance to EGFR TKIs than EGFR WT tumors. The higher mutation burden in EGFR WT tumors compared to those harboring EGFR WT mutations was further confirmed through analysis of TCGA data. Recurrently altered genes shared in the pre- and AR specimens include TP53, EGFR and AKT1/2. Alterations in EGFR (T790M), MYC, WHSC1L1, AXL, MET, HGF, MYC and NTRK1 were found at exclusively at AR. Conclusion: Collectively, these data provide valuable insight into the mutational landscape of EGFR mutant NSCLCs as they evolve on TKIs and identify potential resistance candidate genes for further investigation.

Keywords: Resistance, Targeted therapy, EGFR

MA16.03 GLOBAL REGISTRY (GLORY): ACTIVITY OF RET-DIRECTED TARGETED THERAPIES IN RET-ARRANGED LUNG CANCERS
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Background: RET is a receptor tyrosine kinase (RTK) receptor that has a gain-of-function mutation in the RET gene in >10% of lung cancers. Previous small phase II studies of RET inhibitors showed promising efficacy for RET-rearranged lung cancers (RET-LC). Methods: The GLORY registry is an international, open-label, single-arm, phase II study designed to assess safety, tolerability and activity of the RET inhibitor olmutinib in patients with RET-LC. Eligible patients were adult patients with histologically confirmed, locally advanced or metastatic RET-LC (EGFR or ALK wild-type), no prior systemic therapy and an ECOG performance status of 0-1. Treatment consisted of oral olmutinib at 300 mg daily adminstered in the morning. Patients were followed up until progression of disease or death. Results: 70 patients have been enrolled (58% male, median age 61 years, 67% Caucasian). Preliminary assessment of 13 patients was performed on 9 November 2016. Among these patients, median number of prior treatments was 2 (range 1-4). The median follow-up was 5 months (range 1-9 months). Clinical responses were assessed based on Response Evaluation Criteria in Solid Tumors (RECIST). One patient had a PR (15%), 11 patients had SD (85%), 1 patient had PD (8%). 4 patients had stable disease >12 months. Conclusion: Olmutinib is well tolerated with manageable adverse effects and shows clinical activity in RET-LC. The median progression-free survival is still immature. The results support the need for further evaluation of olmutinib in RET-LC.

Keywords: RET, TARGETED THERAPY IN RET-ARRANGED LUNG CANCERS
Background: EGFR tyrosine kinase (TKI) showed better progression free survival (PFS) in EGFR-mutant non-small cell lung cancer (NSCLC), but the overall survival (OS) benefit was not clear so far. Treatment sequence may contribute to OS, but there is little data so far. We aimed to analyze the impact of treatment sequence of EGFR TKI and chemotherapy on outcomes in EGFR-mutant NSCLC.

Methods: Among NSCLC patients who had EGFR exon 18–21 mutation test results between 2009 and 2014 at Seoul St. Mary's Hospital, 114 patients who had recurrent or metastatic disease, EGFR mutation positive excluding T790M mutation, and received both EGFR tyrosine kinase inhibitor (TKI) and chemotherapy as the 1st or 2nd line of treatment were included. Patients were categorized into two groups according to the treatment sequence: 1st line EGFR TKI followed by chemotherapy (group A), 1st line chemotherapy followed by EGFR TKI (group B). The median follow-up duration was 64.6 (I.B: 20.2–28.8) months. Results: Among total 114 patients, 69 patients received EGFR TKI first and then chemotherapy (group A), and the remaining 45 patients received vice versa (group B). Group A was younger (P = 0.029) and less frequently received platinum-doublet agents than Group B (P < 0.001). Performance status and EGFR mutation status were not different. Overall response or disease control rate were significantly better for EGFR TKI followed by chemotherapy compared to chemotherapy regardless of treatment sequence. However, PFS on both treatment were longer in group B (P = 0.008), especially for patients with exon 19 deletion (P = 0.002). On multivariate analyses, performance status (P = 0.006 for PFS, P < 0.001 for OS) and treatment sequence (hazard ratio (HR) = 3.51, 95% CI: (1.74–7.08)) were related to prognosis.

Conclusion: For exon 19 deletion subtype of EGFR-mutant NSCLC patients, the sequence of cytotoxic chemotherapy followed by EGFR TKI showed better PFS comparing with the reverse sequence, EGFR TKI followed by cytotoxic chemotherapy. We will present the data from larger cohorts the WCLC meeting.

Keywords: non-small cell lung cancer, EGFR mutation, treatment sequence
responses) and disease control rate (DCR) was 44% and 85% respectively. In the dose cohorts between 150 mg BID and 300 mg BID (n=95 pts), the ORR and DCR were 51% and 89%. PK shows rapid absorption with a T_max of 2-4 h and a median T1/2 of 8 h. At 300 mg BID, total 32 patients were treated and ORR and DCR are 53% and 90% respectively. Based on the efficacy, safety and PK results, the 300 mg BID was selected as RP2D. The phase II, AEGIS-1 study has started. The phase II result will be presented. Conclusion: AC0010 shows a safe profile and antitumor activity against T790M mt NSCLC. Phase II, AEGIS-1 study is ongoing to evaluate therapeutic outcomes as a second line treatment for T790M positive NSCLC patients. Clinical trial information: NCT02330367

Conclusion: 300 mg BID was selected as RP2D. The phase II, AEGIS-1 study has started. The 53% and 90% respectively. Based on the efficacy, safety and PK results, the AC0010 shows a safe profile and antitumor activity against T790M mt NSCLC. Phase II, AEGIS-1 study is ongoing to evaluate therapeutic outcomes as a second line treatment for T790M positive NSCLC patients.

Keywords: Phase II/I study, NSCLC, T790M, AC0010

MA16.07 DRUG REPURPOSING TO OVERCOME DE NOVO RESISTANCE OF NON-TRADITIONAL EGFR MUTATIONS
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This abstract is under embargo until December 3, 2016 at 07:00 CET.

MA16.08 MET RESISTANCE OF NON-TRADITIONAL EGFR MUTATIONS

Background: MET alterations leading to exon 14 skipping occur in ~4% of squamous nonsmall cell lung cancer (NSCLCs) and 20–30% of squamous cell lung carcinomas, resulting in MET activation and sensitivity to MET inhibitors in vitro.1-4 Crizotinib, initially developed as a MET inhibitor, is currently approved for the treatment of ALK-rearranged and ROS1-rearranged advanced NSCLC. We present crizotinib antitumor activity and safety data in patients (pts) with MET exon 14-altered advanced NSCLC. Methods: Advanced NSCLC patients positive for MET exon 14-alteration status determined locally by molecular profiling were enrolled into an expansion cohort of the ongoing phase I PROFILE 1001 study (NCT00585195) and received crizotinib at a starting dose of 250 mg BID. Objective responses were assessed using RECIST v1.0. Results: As of the data cut-off of Feb 01, 2016, 38 pts, for an objective response rate of 44% (95% CI: 22–69); 9 pts had stable disease. Median time to response was 7.8 weeks (range: 7.0–16.3), which was the approximate time of the scheduled first on treatment tumor scans for patients. Median progression-free survival could not be calculated. The most common (≥25%) treatment-related AEs (TRAEs) were edema (43%) diarrhea (33%), nausea (33%), vision disorder (33%), and vomiting (29%). Most TRAEs were grade 1/2 in severity and consistent with the known safety profile of crizotinib. Four grade 3 TRAEs (edema, bradycardia, anemia, and weight increased) and no grade 4 or 5 TRAEs were reported. Enrollment of pts with MET exon 14-altered NSCLC continues, and updated data will be available at the time of presentation. Conclusion: Crizotinib has clinically meaningful antitumor activity in pts with MET exon 14-altered advanced NSCLC. The drug has a tolerable AE profile, consistent with that previously reported for pts with ALK-rearranged or ROS1-rearranged advanced NSCLC. Further study of crizotinib in this pt population is warranted.

Keywords: non-small cell lung cancer, crizotinib, MET

MA16.10 LUNG-MAP (S1400) LUNG MASTER PROTOCOL: ACCRUAL AND GENOMIC SCREENING UPDATES
Vassiliki Papadimitriou,1 Mary Redman,2 Fred R. Hirsch,3 Philipp Mack,4 Hossein Borghaei,2 Corey Langer,1 James Wade,1 Martin Edelman,1 Kathy Albain,5 Primo Lara,5 Charu Aggarwal,5 Mark Socinski,6 Scott Gettinger,7 Lyudmila Bazhenova,7 Shakun Malik,7 Vincent Miller,7 Shannon Mcdonough,7 Ellen V. Siga,8 Karen Kelly,9 Roy Herbst10

1MD Anderson Cancer Center, Houston/TX/United States of America, 2Friends of Cancer Research, Washington/DC/United States of America, 3Division of Hem-Oncology, UC Davis Comprehensive Cancer Center, Sacramento/CA/United States of America, 4Department of Hematology Oncology, University of Pennsylvania Health System, Philadelphia/PA/United States of America, 5The Lung-MAP trial, activated June 16, 2014, for the treatment of advanced NSCLC pts positive for MET activation and sensitivity to MET inhibitors in vitro.1-4 Crizotinib, initially developed as a MET inhibitor, is currently approved for the treatment of ALK-rearranged and ROS1-rearranged advanced NSCLC. The drug has clinically meaningful antitumor activity in pts with MET exon 14-altered advanced NSCLC. The drug has a tolerable AE profile, consistent with that previously reported for pts with ALK-rearranged or ROS1-rearranged advanced NSCLC. Further study of crizotinib in this pt population is warranted.

Keywords: non-small cell lung cancer, crizotinib, MET
Treatment results are not yet available as patients continue to accrue. Clinical alterations in SCCA and reveal intermediate or high TMB in most (80.2%) pts. expedite drug registration, confirm anticipated prevalence of targeted Genomic screening is feasible as part of this master protocol designed to ≥96 (15.1%) high (≤5 mutations Mb), 415 (65.1%) intermediate (6-19 mutations/Mb), and 96 (15.1%) high (≥20 mutations/Mb). The median TMB was 10.1.

Conclusion: Genomic screening is feasible as part of this master protocol designed to expedite drug registration, confirm anticipated prevalence of targeted alterations in SCA and reveal intermediate or high TMB in most (80.2%) pts. Treatment results are not yet available as patients continue to accrue. Clinical trial information: NCT02154490.

Keywords: genomic screening, umbrella trial, S1400, Squamous cell lung cancer

MA16: NOVEL STRATEGIES IN TARGETED THERAPY WEDNESDAY, DECEMBER 7, 2016 - 14:15-15:45

MA16.11 CNS RESPONSE TO OSIMERTINIB IN PATIENTS WITH T790M-POSITIVE ADVANCED NSCLC: POOLED DATA FROM TWO PHASE II TRIALS

Glenwood Goss1, Chun-Ming Tsai1, Frances Shepherd2, Myung-Ju Ahn3, Lyudmila Bazhenova4, Lucio Ciro1, Filippo De Marinis1, Enriqueita Felpi5, Alessandro Morabito6, Rachel Hodge6, Mireille Cantarini6, Tetsuya Mitsudomi1, Pasi Jänne1, James Chih-Hsin Yang7

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Background: Brain metastasis in non-small cell lung cancer (NSCLC) develops in 20-40% of all patients and represents a major cause of NSCLC morbidity and mortality. The mechanisms driving metastatic potential across the blood-brain barrier remain poorly understood. Methods: Affymetrix microarray was performed on RNA extracted from 75 pairs of snap-frozen primary lung adenocarcinoma and matched normal lung tissue. Changes in gene expression from the primary lung adenocarcinomas that did not ever metastasize to brain over up to 15 years of follow up were compared to the lung adenocarcinomas that ultimately seeded a brain metastasis. From these 75 patients, tissue from 5 paired snap-frozen brain metastases was also available and gene expression changes between the primary lung adenocarcinomas and matched brain metastases were investigated to identify genes and pathways of interest in the development of brain metastasis. Affymetrix Transcriptome Analysis Console software was used for data analysis and interpretation with fold changes ≥2.0 and p-value of ≤0.05 for significance. Results: From the 75 patients 20 (27%) ultimately developed a brain metastasis from their primary lung adenocarcinoma and 55 (73%) were followed long term without development of brain metastasis. Microarray identified 71 genes that were differentially expressed in lung adenocarcinomas that later produced brain metastasis. S100 calcium binding protein, RAP1GAP, GPR160, and immunoglobulins were among the upregulated genes in primary lung adenocarcinomas that developed brain metastasis. Within the matched sets of brain metastasis, hierarchical clustering showed clear distinction in expression patterns comparing brain metastasis versus normal lung, as well as primary adenocarcinomas versus normal lung. 267 genes were identified to be significantly differentially expressed between paired brain metastasis and primary lung adenocarcinomas. Significant changes in focal adhesion, angiogenesis, matrix metalloproteinase pathways, and immunoglobulins were found in the brain metastasis compared with the paired primary lung tumor. Conclusion: This study represents the largest microarray analysis of snap-frozen pairs of primary lung adenocarcinoma and brain metastasis to date. S100 calcium binding protein, RAP1GAP, GPR160 genes, immunoglobulins, and focal adhesion, angiogenesis, and matrix metalloproteinase pathways were among the upregulated genes in primary lung adenocarcinomas that developed brain metastasis.

Keywords: Metastasis pathways, lung adenocarcinoma, RNA microarray, Brain metastasis

MA17: GENETIC DRIVERS WEDNESDAY, DECEMBER 7, 2016 - 14:15-15:45

MA17.01 MICROARRAY IDENTIFICATION OF GENETIC DRIVERS OF BRAIN METASTASIS IN LUNG ADENOCARCINOMA

Gavitt Woodard1, Vivianne Ding2, Matthew Rosenblum3, Fleur Leguay4, Clara Zoon-Besselink5, Kirk Jones6, Tasha Lea7, Michael Mcdermott8, Ji-jin Kim9, David Jablons2


Background: Brain metastasis in non-small cell lung cancer (NSCLC) develops in 20-40% of all patients and represents a major cause of NSCLC morbidity and mortality. The mechanisms driving metastatic potential across the blood-brain barrier remain poorly understood. Methods: Affymetrix microarray was performed on RNA extracted from 75 pairs of snap-frozen primary lung adenocarcinoma and matched normal lung tissue. Changes in gene expression from the primary lung adenocarcinomas that did not ever metastasize to brain over up to 15 years of follow up were compared to the lung adenocarcinomas that ultimately seeded a brain metastasis. From these 75 patients, tissue from 5 paired snap-frozen brain metastases was also available and gene expression changes between the primary lung adenocarcinomas and matched brain metastases were investigated to identify genes and pathways of interest in the development of brain metastasis. Affymetrix Transcriptome Analysis Console software was used for data analysis and interpretation with fold changes ≥2.0 and p-value of ≤0.05 for significance. Results: From the 75 patients 20 (27%) ultimately developed a brain metastasis from their primary lung adenocarcinoma and 55 (73%) were followed long term without development of brain metastasis. Microarray identified 71 genes that were differentially expressed in lung adenocarcinomas that later produced brain metastasis. S100 calcium binding protein, RAP1GAP, GPR160, and immunoglobulins were among the upregulated genes in primary lung adenocarcinomas that developed brain metastasis. Within the matched sets of brain metastasis, hierarchical clustering showed clear distinction in expression patterns comparing brain metastasis versus normal lung, as well as primary adenocarcinomas versus normal lung. 267 genes were identified to be significantly differentially expressed between paired brain metastasis and primary lung adenocarcinomas. Significant changes in focal adhesion, angiogenesis, matrix metalloproteinase pathways, and immunoglobulins were found in the brain metastasis compared with the paired primary lung tumor. Conclusion: This study represents the largest microarray analysis of snap-frozen pairs of primary lung adenocarcinoma and brain metastasis to date. S100 calcium binding protein, RAP1GAP, GPR160 genes, immunoglobulins, and focal adhesion, angiogenesis, and matrix metalloproteinase pathways were among the upregulated genes in primary lung adenocarcinomas that developed brain metastasis.

Keywords: Metastasis pathways, lung adenocarcinoma, RNA microarray, Brain metastasis

MA17.02 GENOME-WIDE COPY NUMBER AND MUTATIONAL ANALYSIS IN LONGITUDINAL BIOPHIES OF MATCHED PRIMARY AND METASTATIC PULMONARY ADENOCARCINOMAS

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Background: Genetic alterations occurring in the primary tumor may be predictive of response to targeted therapy in patients with metastatic disease. We have previously identified recurrent alterations in the primary tumor that were predictive of clinical benefit of targeted therapy in the brain. The aim of this study was to identify recurrent alterations in the brain that were predictive of clinical benefit. Methods: We used a panel of 460 cancer-related genes to perform targeted re-sequencing on paired brain metastases and matched primary tumors from 20 patients with adenocarcinoma of the lung. Results: We identified 24 recurrent alterations in the primary tumor that were associated with clinical benefit to targeted therapy in the brain. Conclusion: These findings provide new insights into the biology of brain metastatic disease and may improve the selection of patients for targeted therapy. Keywords: Brain metastasis, lung adenocarcinoma, genetics, targeted therapy
Background: There are still limited data on the extent of intratumoral heterogeneity of cancer gene mutations and genome-wide copy number aberrations between primary tumors and metastases in non-small cell lung cancers (NSCLC). Deconvolution of the intertumour of tumor and stromal components remains a major challenge for such analysis. To overcome these limitations, we applied a refined nuclei flow sorting approach on matched longitudinal biopsies (primary/metastasis) from pulmonary adenocarcinomas.

Methods: Multiparameter Ploidy Profiling (MPP) comprises the isolation of nuclei from frozen or formalin-fixed and paraffin embedded (FFPE) tissues, followed by multiparameter flow sorting by DAPI for DNA content (ploidy) and TTF1 as a lineage marker to enrich for tumor cell nuclei. Homogenous TTF1 expression was ascertained by immunohistochemistry. Sorted populations were subjected to genomic profiling by high resolution aCGH and NGS with the Ion Torrent™ Comprehensive Cancer Panel. This approach allows for the detection of genome-wide copy number aberrations and provides all exon-coverage of 405 well-known cancer genes. Sequencing was performed with a mean depth of 965x. MPP was successfully applied on over 60 frozen or FFPE tissue specimens from 19 patients. Clonally unrelated secondary primaries were found in three patients, defined by the absence of both shared copy number (CN) transition and somatic mutations. The concordance rate between primary tumors and corresponding metastases was 65.2% and the presence of at least two evolutionary patterns: 1) early/branched and 2) late/linear progression, with a continuum from high to low genetic divergence over time and space. Taken together, our data suggest macroevolutionary shifts over time and space. Our data argue for a high concordance rate of mutations and CN transitions between primary tumors and their corresponding metastases. Intriguingly, the ploidy remains remarkably stable during progression even after long time-periods, which suggests chromosomal stability with a limited degree of macroevolutionary shifts over time and space. Taken together, our data suggest the presence of at least two evolutionary patterns: 1) early/branched and 2) late/linear progression, with a continuum from high to low genetic divergence of the primary tumor and metastases to their most recent common ancestor.

Keywords: flow sorting, longitudinal, genomic, aCGH

**Methods:** 94 tumor samples originating from 45 clinically considered multiple primary lung cancer patients (including multiple solid tumors and multifocal tumors) were available for genomic alteration analysis (NCT02833467). DNA and RNA were extracted from fresh tumor tissue or formalin-fixed, paraffin-embedded tissue. 143 cancer-related genomic alterations including single nucleotide variations (SNVs), short insertions and deletions (Indels), copy number variations (CNVs) and gene rearrangements were identified by Oncomine Comprehensive Panel (OCP), Ion Torrent techniques. High frequency clinical relevant mutations (EGFR, KRAS, BRAF, PIK3CA) were identified in circulating tumor DNA by droplet digital PCR (ddPCR)

**Results:** The mean age of the patients was 61 years and 71% were female. 91% of patients were stage I. Molecular analysis performed with a good quality. One hundred and thirty-six mutations and twenty four fusions were detected. Alterations were found in 81 of the 94 lesions (86%), involving EGFR (50.0%), TP53 (10.6%), KRAS (8.5%), BRAF (4.3%), RET (7.4%), NF2 (2.1%), CDKN2A (2.1%), APC (5.3%), ATM (5.3%), etc. Forty-two (93.3%) patients harbored discordant gene distribution between multiple tumors. CNVs were much higher in patients with more than 2 lesions. Forty-eight lesions harbored detectable somatic mutations by ddPCR, in which 30(62.5%) lesions were identified positive in circulating tumor DNA. 76.9% (20/26) solid dominant lesions were positive, which is significantly higher than ground glass opacity(GGO) dominant lesions (45.5%, 10/22, p=0.037). Conclusion: Targeted NGS by OCP is feasible to detect multiple mutations simultaneously in early stage multiple primary lung cancers. Circulating tumor DNA has the ability to detect discordant somatic mutations and may represent of the overall mutational load and inter-tumor heterogeneity in multiple solid lung tumors.

**Keywords:** circulating tumor DNA, lung cancer, multiple primary lung cancer

**MA17 GENETIC DRIVERS**

**MA17.03 IDENTIFYING GENOMIC ALTERATION AND INTER-TUMOR HETEROGENEITY OF MULTIPLE PRIMARY LUNG CANCERS BY TARGETED NGS OF TUMOR TISSUE AND CTDNA**

**Kezhong Chen1, Jingbo Zhang2, Wei Chen1, Fan Yang1, Jiangqiao Cai1, Feng Lou1, Xin Wang1, Mingyu Zhao1, Jay Zhang1, Jun Wang2**

1Thoracic Surgery, Peking University People’s Hospital, Beijing/China, 2San Valley Biotechnology Inc, Beijing/China

**Background:** Evidence supports the existence of genomic discrepancy in multiple primary lung cancers (MPLC). This study identified genomic alterations of MPLC by targeted next-generation sequencing (NGS) and assessed whether inter-tumor heterogeneous somatic mutations could be detected in circulating tumor DNA (ctDNA).

**Methods:** 94 tumor samples originating from 45 clinically considered multiple primary lung cancer patients (including multiple solid tumors and multifocal tumors) were available for genomic alteration analysis (NCT02833467). DNA and RNA were extracted from fresh tumor tissue or formalin-fixed, paraffin-embedded tissue. 143 cancer-related genomic alterations including single nucleotide variations (SNVs), short insertions and deletions (Indels), copy number variations (CNVs) and gene rearrangements were identified by Oncomine Comprehensive Panel (OCP), Ion Torrent techniques. High frequency clinical relevant mutations (EGFR, KRAS, BRAF, PIK3CA) were identified in circulating tumor DNA by droplet digital PCR (ddPCR).

**Results:** The mean age of the patients was 61 years and 71% were female. 91% of patients were stage I. Molecular analysis performed with a good quality. One hundred and thirty-six mutations and twenty four fusions were detected. Alterations were found in 81 of the 94 lesions (86%), involving EGFR (50.0%), TP53 (10.6%), KRAS (8.5%), BRAF (4.3%), RET (7.4%), NF2 (2.1%), CDKN2A (2.1%), APC (5.3%), ATM (5.3%), etc. Forty-two (93.3%) patients harbored discordant gene distribution between multiple tumors. CNVs were much higher in patients with more than 2 lesions. Forty-eight lesions harbored detectable somatic mutations by ddPCR, in which 30(62.5%) lesions were identified positive in circulating tumor DNA. 76.9% (20/26) solid dominant lesions were positive, which is significantly higher than ground glass opacity(GGO) dominant lesions (45.5%, 10/22, p=0.037). Conclusion: Targeted NGS by OCP is feasible to detect multiple mutations simultaneously in early stage multiple primary lung cancers. Circulating tumor DNA has the ability to detect discordant somatic mutations and may represent of the overall mutational load and inter-tumor heterogeneity in multiple solid lung tumors.

**Keywords:** circulating tumor DNA, lung cancer, multiple primary lung cancer
Background: Morphological and genetic heterogeneity predict prognostics, impede continuous responses to systemic regimens and foster inevitable treatment failure. But how morphological and genetic features evolve in tumorigenesis still remains controversial.

Methods: Single (n=1112) and multiple (n=91) primary adenocarcinoma patients receiving surgeries with specific prominent subtypes were screened. Six patients with mixed ground glass opacities and maximum cross-sections of primary tumors were randomly selected. Intra-tumoral regions with different subtypes and imaging densities related to relative distributions, were resected for target region sequencing and further molecular evolutionary analyses.

Results: Clinical data revealed certain preferences of driver gene mutations and discrepant survival benefits. Driver gene heterogeneity was higher in multiple primary lung cancers (51.7%, 15/29) than single ones (1.4%, 1/70). Copy number alterations implied more consistence within the same subtype and tended to be higher in lepidic subtype. Somatic nucleotide variants revealed highest homogeneity between different regions within the same tumor lesion. Sequencing data indicated larger fractions of geographically ubiquitous mutations than pathologically ones, and higher mutation frequencies of shared mutations in the lepidic than acinar subtype. Phylogenetic trees exhibited higher geographically private mutation burdens of lepidic than acinar region in lesions with mixed subtypes; while in lesions with the same subtype, the central region bore higher mutation burdens than in the periphery, implying a linear accumulation of genetic mutations. Functional analyses of private mutations verified that lepidic subtypes promoted intracellular organism and structure development, promoting growth and proliferation. Acinar subtypes lead to metabolic and signaling transduction pathway. Preferences of divergent pathway alterations delineated branched evolutions from low to higher grade subtypes.

Conclusion: We propose a model that the same morphological subtype evolves with a linear accumulation and mixed subtypes in branched evolutionary trajectories with preferences to pathway alterations. Couple with relatively geographical distributions of different subtypes, tumor microenvironment might contribute more to genetic instability and thus tumor evolutions.

Keywords: pulmonary adenocarcinoma, morphology, Genetic evolution, Predominant subtypes
MA17.06 LANDSCAPE OF SOMATIC MUTATIONS INVOLVING LUNG CANCER ASSOCIATED GENES IN NON- SMALL CELL LUNG CANCER (NSCLC) PATIENT-DERIVED XENOGRAFTS

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Background: Patient derived xenografts (PDXs) have high fidelity to their histological origins, and maintain the molecular heterogeneity and genetic aberrations of the donor patient tumors more faithfully than established in non-small cell lung cancer (NSCLC) cell lines. This study aimed to evaluate whether our panel of PDX models recapitulate known cancer-related gene mutations. Methods: Whole-exome sequencing was performed on 103 NSCLC PDX models, 47 adenocarcinoma (AdC) and 56 squamous (SqCC), with a mean coverage of 8x. After filtering for contaminating mouse reads, the exome data were aligned using the Burrows-Wheeler Aligner, processed using the standard GATK pipeline, and mutations were identified using MuTect. Additional filtering using dbsNP, ExAC and ESP was performed for samples without corresponding normal lung exome data (n = 80). The identified mutations were compared to 1260 frequently mutated cancer-related genes, which were compiled from a panel of cancer-related mutated genes (555) and a panel of lung cancer-specific mutated genes (1082). Results: High rates of somatic mutations were observed in both AdC (mean of 12.4 mutations/megabase) and SqCC (mean of 11.7 mutations/megabase) PDX models. Compared to the rates observed in primary lung cancers in The Cancer Genome Atlas studies (mean of 8.9 mutations/megabase in AdC; 8.1 mutations/megabase in SqCC), these values appear higher, but may be inflated due to the lack of data from corresponding normal tissues. AdC models had a total of 953 mutated genes (median: 57 genes/model; range: 5-307), while SqCC models were characterized by 1007 mutated genes (median: 55 genes/model; range: 21-315). Specific mutation frequencies were compared to those determined in a recent study involving genomic alterations in human primary lung AdC and SqCC (Nature Genetics 2016; 48; 607-616). This comparison, based on mutated genes common in both studies, demonstrated significant correlation of the frequencies in 791 genes in AdC (ρ = 0.78; p < 2.2 x 10^-16), as well as in 799 genes in SqCC (p = 0.73; p < 2.2 x 10^-16). Three genes that were reported as significantly mutated in both AdC and SqCC primaries, and had higher mutation frequencies in SqCC were also observed to be higher in both our ScC PDX models (TP53: 4.8% in AdC vs. 55.4% in SqCC; CDKN2A: 4.3% vs. 7.1% and PIK3CA: 2.1% vs. 23.2%); however, the statistical significance of these differences needs to be tested. Conclusion: Mutation landscapes in cancer genes are recapitulated in AdC and ScC PDX models. The fidelity of these landscapes in matched patient primary tumors is being investigated.

Keywords: Somatic mutations, PDX, whole-exome sequencing, NSCLC
MA17: GENETIC DRIVERS
WEDNESDAY, DECEMBER 7, 2016 - 14:15-15:45

MA17.10 YES1 Kinase is a New Therapeutic Target in Non-small Cell Lung Cancer

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Background: Next-generation sequencing techniques have allowed the discovery of driver mutations in non-small cell lung cancer (NSCLC), that can be translated into advances in cancer diagnosis and treatment. However, specific oncogenic alterations are still unknown in a high proportion of NSCLC patients, that therefore cannot benefit from targeted therapies. The challenge is to identify new genetic alterations that allow the use of molecular-targeted therapies. In previous studies from our group (Aramburu et al. BMC Genomics 2015), the analysis of tumor molecular profiles from patients with NSCLC allowed us to identify the DNA copy number amplification of YES1 kinase (v-YES1 Yamaguchi sarcoma viral oncogene homolog 1) as a prognostic marker in lung cancer. YES1 kinase is member of the Src family of non-receptor protein tyrosine kinases that are involved in the regulation of cell growth, apoptosis, cell-cell adhesion, cytoskeleton remodeling, and differentiation. The aim of this project is to evaluate if YES1 is a driver gene in NSCLC, and if targeting its activation may be a potential new therapeutic strategy. Methods: We first evaluated the prognostic role of YES1 protein expression in two independent series of 76 and 234 NSCLC patients, respectively. In both series, the multivariate analysis revealed that high YES1 expression is an independent poor prognostic factor for overall survival (CUN series HR: 3.416 [0.933-12.508]; MD Anderson series HR: 1.570 [1.032-2.391]). We next evaluated the effect of YES1 knockdown in 5 NSCLC cell lines with YES1 amplification and overexpression, and in 3 cell lines without YES1 amplification and with low protein expression. YES1 downregulation by two specific siRNAs decreased proliferation and cell survival only in those cells overexpressing YES1. Congruently, YES1 inhibition led to apoptosis only in those cells. Results: Consistent with these results, constitutive overexpression of YES1 in cells with low YES1 expression significantly enhanced cell proliferation. We next evaluated the effect of the multitarget Src kinase inhibitor dasatinib on the proliferation of NSCLC cell lines with high (8 cell lines) or low (4 cell lines) YES1 expression. Dasatinib dramatically inhibited proliferation in high YES1-expressing cell lines, whereas low YES1 cell lines were more resistant to dasatinib treatment (G1/S phases were four orders of magnitude higher in resistant cells). Conclusion: In conclusion, our results indicate that YES1 is a promising therapeutic target in NSCLC. Furthermore, amplification and high expression of YES1 may define a subset of patients who may potentially benefit from dasatinib treatment.

Conclusion: Our study demonstrates that knockdown of Akt2 suppresses tumorigenesis by attenuating cell proliferation, increasing apoptosis and interfering cell cycle in non-small cell lung cancer. Raf1 overexpression partly offsets these effects by enhancing cell proliferation, suppressing apoptosis and affecting downstream proteins. Thus, there may be existing Akt2/Raf1 pathway in NSCLC, which plays an important role in tumorigenesis.

Keywords: Akt2, Raf1, Cell signal pathways, NSCLC

MA17.11 KNOCKDOWN OF AKT2 SUPPRESSES TUMORIGENESIS AND RAF1 OVEREXPRESSION OFFSETS THIS EFFECT IN NON-SMALL CELL LUNG CANCER

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Background: Akt2 (Protein Kinase B isoform 2) is an essential protein, which is involved in tumor cell proliferation, differentiation, motility, and cell death in non small cell lung cancer (NSCLC). Raf1 is also a key protein regulating the functions in NSCLC. However, the relationships between Akt2 and Raf1 are unknown. This study aimed to investigate the influence of Akt2 knockdown and its interaction with overexpression Raf1 in non-small cell lung cancer cells. Methods: Small interfering RNA was used to knockdown Akt2 and lentivirus was introduced to overexpress Raf1 in H1299, A549, Sk-mes and H460 cell lines. Western blot was performed to investigate expression levels of relevant proteins in the pathway. Cell survival, proliferation and apoptosis were evaluated in vitro and vivo. Then, we examined Akt2 and Raf1 expressions via immunohistochemistry (IHC) in 65 NSCLC patients. Results: Knockdown of Akt2 suppressed cell proliferation, arrested tumor cells in G0/G1 phase and induced apoptosis in all cell lines distinctively. Raf1 phosphorylation was also inhibited after Akt2 knockdown in the cell lines. When Raf1 overexpression combined with Akt2 knockdown in these cell lines, cell proliferation was enhanced, and apoptosis rates were decrease compared with Akt2 knockdown alone. These trends were also observed in vivo experiments. Furthermore, the downstream proteins of Raf1, such as MEK, ERK, p-MEK and p-ERK were observed decrease in Akt2 knockdown groups. Of all NSCLC specimens, Akt2(-)/Raf1(+) patients had the worst prognosis of 5-year overall survivals.

Conclusion: Our study demonstrates that knockdown of Akt2 suppresses tumorigenesis by attenuating cell proliferation, increasing apoptosis and interfering cell cycle in non-small cell lung cancer. Raf1 overexpression partly offsets these effects by enhancing cell proliferation, suppressing apoptosis and affecting downstream proteins. Thus, there may be existing Akt2/Raf1 pathway in NSCLC, which plays an important role in tumorigenesis.

Keywords: Akt2, Raf1, Cell signal pathways, NSCLC
P1.01-001 REDUCTION OF CIGARETTE CONSUMPTION THROUGH A NATIONAL POLICY FOR TOBACCO CONTROL IN BRAZIL

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Background: According to WHO, "approximately one person dies every six seconds due to tobacco, accounting for one in 10 adult deaths. Up to half of current users will eventually die of a tobacco-related disease", which can be lung cancer (87%), pulmonary disease (61%) and coronary heart disease (32%), considering secondhand smoke exposure too as says the Surgeon General’s Report. To protect the health of the Brazilian population, the government has been applying measures, since the 90s, to reduce the harm caused by tobacco use because they have committed to reduce the premature mortality from tobacco use in 30% from 2013 to 2025, to achieve one of the nine voluntary WHO Global NCD’s Targets. Methods: Quantitative secondary data analysis confronting the cigarette prevalence rates found in Risk and Protective Factors Surveillance System of Chronic Diseases Telephone Surveys (VIGITEL) and the National Policy for Tobacco Control measures. Results: Before ratifying the WHO Framework Convention on Tobacco Control, in 1996 the government started promoting smoke-free places, banning the advertising, promotion and sponsorship, that were finally regulated in 2014. In 2011, the Secretariat of Federal Revenue developed a new system for cigarette taxation to establish a minimum price for a pack of twenty cigarettes and raise the cigarette’s excise tax gradually. In May, 2016 the total taxation represents 76% of the cigarette price and will bring to 81% after December 2016. This is one of the measures of the Framework Convention for Tobacco Control/WHO more cost-effective in the country. Article 6, which deals with the rising prices and taxes on tobacco products to reduce demand. Several surveys and studies point to a reduction in smoking prevalence. Every year, since 2006, the VIGITEL report has shown prevalence rates collected in the entire adult population of the 27 state capitals. In 2015 the frequency of smokers decreased to 10.4%, compared to 2006 which were 15.2% for both sexes. The report also indicated the effectiveness of the prices and taxes measure, when you compare the frequency of former smokers with lower education, those representing people with lower income. In 2006 they were 25.6%, and in 2015 they increased to 29.1%. Conclusion: The present study shows a prevalence decline as a positive result coming from the National Policy for Tobacco Control implementation between the years of 2006 and 2015. To achieve the WHO Global NCD’s Target we still have too much work to do, specially protect the National Policy from the tobacco industry interference.

Keywords: WHO FCTC, Tax and Price, Consumption, Tobacco Control

POSTER SESSION 1: P0.01: EPIDEMIOLOGY, TOBACCO CONTROL AND CESSATION/ PREVENTION TOBACCO, RADON, AIR POLLUTION, OTHER RISK FACTORS – MONDAY, DECEMBER 5, 2016

P1.01-002 ENVIRONMENTAL TOBACCO SMOKE EXPOSURE AND EGFR MUTATIONS/ALK TRANSLOCATION IN NEVER SMOKERS. A MULTICENTRE STUDY IN SPANISH NEVER-SMokers

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Background: Mutations or translocations in driver genes of lung cancer such as EGFR or ALK are important treatment targets for advanced lung cancer. These alterations are present mainly in never-smokers. Exposure to environmental tobacco smoke (ETS) might provide some explanation to the presence of such genetic traits. Furthermore, ETS exposure might have a different effect should occur at home in adult life, during childhood, or at work. We aim to know if ETS exposure is associated with EGFR mutations or ALK alterations in a huge sample of never smoking lung cancer cases. Methods: We recruited never smoking lung cancer cases diagnosed consecutively in 9 Spanish Hospitals since 2011. We collected extensive information on different lifestyle activities and also measured residential radon exposure. Cases had to be older than 30 years with no upper age limit and with no previous history of cancer. A never smoker was defined as: 1) an individual who smoked less than 1 daily cigarette for no more than 6 months or, 2) no more than 100 cigarettes smoked in lifetime. EGFR mutations and ALK alterations were determined using standard procedures. Logistic regressions were performed to analyze the influence of exposure to ETS in different settings (adult life at home, at work or during childhood). The dependent variables were EGFR mutation (of any type) or not, or ALK translocation (present/absent). Results were adjusted by age, gender and residential radon exposure. Results: We included 389 never smoking lung cancer cases. 80.5% were females and the median age was 71 and the interquartile range 61-78 years. 246 patients had EGFR determined (63.2% of the total) and of them, EGFR was mutated in 43%. ALK status was determined in 97 patients (24.9% of the total), and was positive in 16 patients (16.5%). Living at home with a smoker for more than 20 years was not associated with EGFR mutation or ALK translocation, and the same occurred for being exposed to ETS at work. When exposure to ETS in childhood (before 16) was considered, we observed that those exposed to ETS had an OR of EGFR mutation of 0.57 (95%CI:0.31-0.95; p=0.07). No association was observed for ALK translocation. Conclusion: These results suggest that exposure to environmental tobacco smoke in childhood might reduce the chance of EGFR mutation in never smokers with lung cancer. This observation would add more evidence to avoid exposure to ETS in any time of life. Funding: ISCIII/P11/01765/Cofinanciado FEDER

Keywords: EGFR, ALK, Environmental tobacco smoke

P1.01-003 NOVEL ASSOCIATIONS BETWEEN LUNG CANCER-RELATED GENES AND INDOOR RADON EXPOSURE

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Background: Although the most important risk factor for lung cancer is smoking, lung cancers in never smokers (LCINS) is being increasingly reported. Thus, studies of other risk factors for lung cancer are needed. Recently, radon (Rn), a natural, noble gas, was recognized as the second most common risk factor for lung cancer. OBJECTIVES

To identify variations in genes associated with lung cancer in never smokers exposed to radon gas. Methods: We conducted an optimized next generation sequencing analysis of lung cancer-related genes in normal and tumor tissues from Korean LCINS patients who had been exposed to radon gas indoors. A total of 926 SNPs showing genome-wide statistical significance were analyzed. Results: Several genes commonly associated with lung cancer, EGFR and TP53 in chromosomes 7 and 17, respectively, showed significant correlations with LCINS. Others included ERG in chromosome 21, RIT in chromosome 1, and BIRC6 in chromosome 2. Meanwhile, several additional loci showed novel associations with LCINS as a result of exposure to radon gas, including PDK1, VHL, WHSC1, CDH4, MBD2, ATRX, CCND1, and PTPRD. Conclusion: Using next generation sequencing, we found several lung cancer-related genes to be associated with tumors in never smokers exposed to radon. Most of the noted loci have not been shown to be associated with lung cancer, and provide new insights into the development of LCINS. Our findings may serve as a reference for replication and validation studies on the prevention and treatment of LCINS as a result of exposure to radon gas. ACKNOWLEDGMENTS: This study was supported by the Korean Ministry of Environment as part of the “Environmental Health Action Program” (grant number 2015001350002).

Keywords: Radon, next generation sequencing, lung cancer in never smoker, genetic variation
alterations in NSCLC patients, but a trend has been suggested in smokers and 3 (6.3%) light smokers. 100% of the patients from India with 11.2% (11.9 million) of world’s smokers has 2 million tobacco users in India, highest globally. Supreme Court of India observed that gutka and pan-masala are food products. Beginning of 2010, all gutka products in India banned gutka and pan-masala containing tobacco. APPREHENSION was raised that ban on ST products will cause switching to smoking by huge ST user population vastly increasing risk of lung-cancer in India. This ban provided natural experiment on which this observational research studied how ban on popular ST products alters pattern of tobacco-use, especially smoking. Findings are expected to be strategically significant to inform future policies. Methods: Questionnaire of Global Adult Tobacco Survey-India (2010), developed by WHO, CDC and Govt. of India was modified to answer research questions and accommodate retrospective-cohort study design. Through 2-step randomization process, 500 households were sampled from Delhi. Participants were adults and interviewed during March-June, 2016, comprehensively, including tobacco-use currently and before gutka-ban. Inbuilt mechanisms in standardized questionnaire cross-validated self-report and minimised recall bias. Data was entered into SPSS and statistically analysed. Results: 94% of 500 households visited agreed to participate. 73.4% of pre-ban gutka-users switched to twin-sachet (pan-masala and chewing-tobacco sold separately by gutka-manufacturers to circumvent law). Delhi’s order bans all ST products. Except premixed gutka, remaining ST products are freely available and consumed. 21.8%switched to khaini or other ST products. A large fraction switched from singledose sachets to multidose sachet. Interestingly, 96.2% respondents believed tobacco as very harmful (84.6%) or somewhat harmful (11.6%). However, only 18.6% gutka users attempted quitting after ban. 6.4% successfully quit. In our sample, we DID NOT find anyone switching to smoking due gutka unavailability. On an opposite thought, one may expect, ban on an ST product (Gutka) will increase awareness and motivate smokers to quit as spillover effect. But it wasn’t observed either. Conclusion: In absence of strong quitting promotion campaign, ban on selective tobacco products has limited role in changing prevalence of tobacco use. If selective ST products are banned, ST users preferentially switch to other available ST products, BUT NOT to smoking. As majority ST users switched instead of quitting (after gutka-ban without simultaneous quitting campaign), we may logically conclude that effective ST product may lead ST users to switch to less favourable option of smoking. This is, however, subject to verification by similar study if there is ever effective ban on all ST products.

Keywords: Smokeless Tobacco, Gutka ban, smoking, GATS

Background: Radon gas is the first cause of lung cancer in non-smoking population. The World Health Organization (WHO) recommends radon concentration lower than 100 Bq/m3. In recent years, most of the advances in personalized therapy in NSCLC patients also occurred in non-smokers. Furthermore, limited information is available about the clinical and pathological characteristics in patients exposed to radon gas. We hypothesized that residential radon could be associated to some specific pathological and molecular alterations in NSCLC patients. Methods: Prospective study of a cohort of NSCLC patients harbouring molecular alterations (EGFR, BRAF mutations, (m), ALK and ROS1 rearrangements (r)) in our unit between September 2009 and October 2015. A radon detector alpha-track was given to each patient to measure residential radon concentration for 3 months; it was analysed using optical microscopy. We collected demographic information, smoking history, environmental exposure and clinical characteristics. The pathologic characteristics were prospectively recorded by a lung cancer pathologist, including histology pattern, grade and inflammatory infiltrate. EGFR and BRAF mutation (m) were analyzed using qualitative real-time polymerase chain reaction (PCR) and ALK and ROS1 rearrangement by fluorescence in situ hybridization (FISH). Data was stored using IBM SPSS software. Results: 60 detections were delivered (10% missing), 48 patients were evaluated (89.6% living in Madrid). Median age 66.5 (29-82); 33 (68.8%) females; 33 non-smokers (31.3% passive smokers and 35.4% childhood exposure) and 3 (6.3%) light smokers. 100% of the patients from India with 11.2% (11.9 million) of world’s smokers has 2 million tobacco users in India, highest globally. Supreme Court of India observed that gutka and pan-masala are food products. Beginning of 2010, all gutka products in India banned gutka and pan-masala containing tobacco. APPREHENSION was raised that ban on ST products will cause switching to smoking by huge ST user population vastly increasing risk of lung-cancer in India. This ban provided natural experiment on which this observational research studied how ban on popular ST products
P1.01-007 A CROSS-SECTIONAL STUDY ON TOBACCO CONSUMPTION PATTERN AMONG AUTO RICKSHAW DRIVERS IN CHENNAI CITY, TAMIL NADU, INDIA

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Background: Tobacco use is a major preventable cause of premature death and diseases, currently leading to five million deaths worldwide which are expected to raise over eight million deaths worldwide by 2030. India is the second largest consumer of tobacco in the world. Tobacco use is leading cause of deaths and disabilities in India as well, killing about 1.2 lakh people in 2010. About 29% of adults use tobacco on a daily basis and an additional 5% use it occasionally. This study is contemplated with an aim to assess the prevalence of tobacco consumption and the associated factors involved in its consumption, as this group of the population is under constant pressure and account for the workforce of the country. So through this study we could be able to know *The reasons of consumption. *Amount of consumption *Awareness of ill effect of tobacco consumption* Out of Pocket expenditure.

Methods: A Cross sectional descriptive study was conducted among Auto Rickshaw Drivers in Chennai City Auto drivers who were working for more than two years and present on the day of examination and who were willing to participate in the study were included. Cluster random sampling technique was used. 400 samples were selected from 40 auto stands of various parts of Chennai City. Data was collected using a Survey Proforma which comprised of a Questionnaire which can assess the frequency of consumption, age of initiation, the amount of consumption, mental stress, economic factors, any past history of disease and most importantly the awareness towards oral cancer. The data recorded was transferred and analysed using SPSS version 20. Chi-square test was used to test the significance between groups.

Results: Prevalence among auto rickshaw drivers for consumption of tobacco products was very high (87%). Auto rickshaw drivers were mostly used tobacco in the form of Gutkha (72%) and bidi (40%) in comparison to other products. In the opinion of auto rickshaw drivers increase in tax may reduce it consumption and the majority of drivers (70%) think that tobacco must be banned. Conclusion: Prevalence of tobacco use among auto rickshaw drivers was very high. Mostly they use tobacco products to reduce stress, to be awake or to remove nervousness but a large number of participants also use them without any reason. Almost one half of the study population was suffering from tobacco related diseases like cough, ulcer on mouth, lung disorder. They are in definite need of tobacco cessation activities.

Keywords: Tobacco, Awareness, Prevalence, Addiction.

P1.01-008 KNOWLEDGE, ATTITUDES, AND SMOKING BEHAVIOURS AMONG DENTAL AND MEDICAL STUDENTS IN CHENNAI, TAMIL NADU, INDIA

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Background: Tobacco use continues to be the leading cause of preventable disease and it is responsible for more than 5 million deaths each year worldwide. Despite this, there are still 650 million smokers in the world. The prevalence of smoking among adults accounts for approximately 25% deaths annually. Smoking remains the main cause of mortality and morbidity in the developing nations. Healthcare professionals have an important role to play both as advisers influencing smoking cessation and as role models. However, many of them continue to smoke. Several studies have demonstrated the efficacy of smoking cessation programs and the importance of physician's advice to their patients. The aims of the present study are as follows: (i) to evaluate smoking prevalence, knowledge and attitudes, and tobacco cessation training (ii) to examine the difference between smokers and non-smokers, (iii) to compare the structured questionnaire consisting of 14 questions related to tobacco/smoking habits, cessation training and role of health professionals in tobacco control were asked to the study population and their response was recorded. Random sampling method was used and data was collected from a cross-sectional survey. The survey was conducted between January and February 2015. Statistical analysis was done using SPSS version 17. Logistic regression model was used to identify possible associations with tobacco smoking status. The level of significance was Results: A total of 259 answered the questionnaire of which 29% declared to be smokers. About 53% of the males have smoked at least once in their life and the age of cigarette initiation was 16-17 years for 28% of the sample. 76% considered healthcare professionals as behavioural models for patients, and 96% affirmed that health professionals have a role in giving advice or information about smoking cessation. Although 87% heard about smoking related issues during undergraduate courses, only 17% received specific smoking cessation training during specialization. 93% of the sample agreed that health professionals should receive specific training on smoking cessation according to while 6% were of the opposite opinion. Conclusion: The present study highlights the importance of focusing attention on smoking cessation training, given the high prevalence of smokers among physicians specializing in medicine and dentistry, their key role both as advisers and behavioural models, and the limited tobacco training offered in the curriculum. In the field of public health, tobacco screening, and intervention is one of the most effective clinical preventive services.

Keywords: Medical students, smoking habits, oral cancer

P1.01-010 AWARENESS AND LUNG CANCER RISK FACTORS AMONG LAY PERSONS AND PHYSICIANS

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Background: Albania is a country with a high prevalence of smoking but a national cancer registry has not been initiated yet and data on lung cancer is scarce. Methods: Aim - Methods: In 2010-2014, 1254 patients presented to our hospital with either symptoms or an abnormal finding in their chest X-ray and were diagnosed with lung cancer. This is a descriptive retrospective study, reporting data on the histological type of cancer and smoking history

Results: Results: Of the 1254 patients, 79% (n=1001) were men and 21% (n=253) women. Age range was 16-89, with mean age in men 62.4±8.5 and in women 58±10. Diagnosis was confirmed by histology (table 1). Regarding NSCLC, 78% of patients had an advanced stage (III and IV). Only 268 patients were non-smokers, 126 were ex-smokers and the remaining 67% (n=860) were current smokers with high exposure (92 pack/years). Day hospital average is 7 day, and day range was [1-21] with SD±6.4. Performance status was: 60.2% improved, 35.2% idem, 3.3% dead in hospital.

Conclusion: In Albania, lung cancer is an increasing pathology and there is a high prevalence of squamous cell carcinoma especially in men, probably associated with the heavy history of smoking and most patients are diagnosed at a late stage. Policies for smoking cessation should be strengthened and a lung cancer screening program should be initiated.
Background: Tobacco consumption, and more specifically active smoking, remains the main risk factor for lung cancer (LC) and continues to be the target of awareness campaigns worldwide. However, in recent decades, other risk factors have been identified, including passive smoking, atmospheric pollution, and occupational exposure. This analysis focuses on awareness of LC risk factors among the lay population and physicians. Methods: The 4th French nationwide observational survey, EDIFICE IV, was conducted by phone interviews of a representative sample of 1602 subjects, aged between 40 and 75 years, from June 12 to July 10, 2014. A mirror survey was also conducted by phone among physicians between July 9 and August 8, 2014. Both surveys were conducted using the quota method on representative samples of 1602 lay persons and 301 physicians. The following analyses were conducted amongst 1463 lay persons with no history of cancer and 301 physicians. Interviewees were asked to cite the five main risk factors for LC. Results: LC risk factors associated with tobacco in general were widely cited in first position by both physicians and the lay population (100% and 96%, respectively; P≤0.01), with the role of active smoking (100% vs 94%, P≤0.01) and passive smoking (77% vs 68%, P≤0.01) clearly identified. Twice as many physicians cited asbestos as a risk factor, ranking it in second place, compared with the lay population (77% vs 36%, P≤0.01). Atmospheric pollution was cited to the same degree by physicians and the lay population (49% vs 43%, P≤0.05), the latter ranking it second. Heredity and family history came fourth (32% vs 13%, P≤0.01) and alcohol (13% vs. 10%, not statistically significant) in both populations. Infections and other respiratory disorders were cited by less than one person in ten (7%). Poor dietary habits were very rarely cited by either physicians or the lay population (1% vs 4%, respectively, P≤0.01). Conclusion: The awareness of risk factors for lung cancer is broadly consistent with the established risk factors, among both physicians and the lay persons in our survey. As expected, tobacco was ranked first, followed by atmospheric pollution and asbestos, though the latter is less present in the mind of the lay population compared to physicians. It is noteworthy that even among physicians, a history of respiratory disorders was only marginally acknowledged.

Keywords: risk awareness, lay population, history of respiratory disorders, risk factors

POSTER SESSION 1 - P1.01: EPIDEMIOLOGY, TOBACCO CONTROL AND CESSATION/PREVENTION
TOBACCO, RADON, AIR POLLUTION, OTHER RISK FACTORS – MONDAY, DECEMBER 5, 2016

P1.01-011 ROFLUMILAST ATTENUATES BENZO(A)PYRENE-INDUCED LUNG CANCER VIA SUPPRESSION OF AIRWAY INFLAMMATION IN MURINE MODEL
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Background: Chronic airway inflammation has been emerging targets for lung cancer chemoprevention as well as treatment of COPD. The aim of the present study was to determine the role of roflumilast and aerosolized budesonide in benzo[a]pyrene-induced lung cancer in mice and to elucidate the possible mechanisms. Methods: Female A/J mice were given a single dose of benzo[a]pyrene. Intraperitoneal administration of roflumilast (1mg/kg, 5mg/kg) began 2 weeks post-carcinogen treatment and continued tri-weekly for 28 weeks. Aerosolized budesonide was administered by aerosol delivery for 2 min/day and 5 days/week. Tumor load was determined by averaging the total tumor volume. Benzo[a]pyrene induced an average tumor size of 9.4 ± 1.8 tumors per mouse, with an average tumor load of 19.5 ± 3.8mm. Roflumilast treatment at 1 and 5 mg/kg did not inhibit tumor number, however, reduced tumor load, an average of 8.8 ± 2.0mm at 5mg/kg treatment, significantly. Aerosolized budesonide administration did not show reductions of tumor number or load. The decreased expressions of cyclic AMP and protein kinase A caused by benzo[a]pyrene were increased by roflumilast treatment. NF-κB expression in tumor tissues was lower in the roflumilast group than the place group. Conclusion: In vivo experiments in the benzo[a]pyrene-induced model of lung cancer show that roflumilast significantly inhibits tumorigenicity via suppression of inflammation. Possible mechanisms between CAMP pathway and lung cancer development will needed to be determined.

Keywords: Roflumilast, budesonide, lung cancer

POSTER SESSION 1 - P1.01: EPIDEMIOLOGY, TOBACCO CONTROL AND CESSATION/ PREVENTION
TOBACCO, RADON, AIR POLLUTION, OTHER RISK FACTORS – MONDAY, DECEMBER 5, 2016

P1.01-012 KAVA EFFECTS ON THE METABOLISM OF TOBACCO-SPECIFIC CARCINOGEN 4-(METHYLNITROSAMINO)-1-(3-PYRIDYL)-1-BUTANONE (NNK) IN HUMANS
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Background: Kava is extracted from the roots of Piper methysticum and is consumed by South Pacific Islanders as a relaxing beverage. Epidemiologic evidence points to a protective effect of kava against tobacco-induced lung cancer. NNK is a potent tobacco-specific carcinogen indisputably linked to lung cancer formation. Kava reduced NNK-induced lung adenoma formation in the A/J mouse model. Data also suggest that enhanced NNAL detoxification may be a potential mechanism by which kava exerts a chemopreventive effect. In humans, urinary NNAL is a validated biomarker of NNK uptake. We conducted a clinical trial in smokers to assess the effect of kava on NNK metabolism. The primary objective was to compare urinary total NNAL before and after kava administration. Secondary objectives included comparing the NNAL glucuronide-to-free NNAL ratio, determining the safety of kava, and quantifying O-methylguanine adducts. The hypothesis was that kava administration would result in increased levels of NNAL in the urine (and increased NNAL-gluc/NNAL-free ratio), reflecting increased elimination and/or increased detoxification of NNK. Additionally, we hypothesized that kava could reduce O-methylguanine adducts. Methods: We conducted a single-arm, open-label clinical trial in adult healthy smokers, in which subjects took a commercial kava supplement three times daily for seven days. Twenty-four hour urine collections were collected at baseline, days 4 and 5, and days 6-7 of the kava intervention for NNAL quantification. Blood samples were collected at baseline, day 4, and day 7 of the kava intervention for safety monitoring and for DNA adduct analysis. Subjects also completed a detailed tobacco questionnaire, food diary, smoking diary, and cigarette evaluation scale (CES) questionnaire. To date, 17 subjects (goal = 18) have completed the study. Results: The results and statistics are being finalized. Short-term kava administration was safe with no evidence of hepatotoxicity. Subjects experienced less of the reinforcing effects of smoking after short-term kava administration as determined by the CES scores. The total CES score decreased on average by 4.47, from 45.53 to 41.06 (p=0.053, 95% CI [0.06-9.01]). Notably, the smoking “satisfaction” scores decreased by 0.67 (p=0.024, 95% CI [0.09-1.12]). Conclusion: This is the first study investigating the effect of kava on NNK metabolism in humans and is the first step to gain a more sophisticated mechanistic understanding of kava’s role in potentially modulating tobacco-related lung cancer risk. Short-term kava administration is safe in healthy adult smokers, Kava had potential as a safe chemopreventive agent for smokers or tobacco cessation aide.

Keywords: Kava, NNK, NNAL, Tobacco smoke

POSTER SESSION 1 - P1.01: EPIDEMIOLOGY, TOBACCO CONTROL AND CESSATION/ PREVENTION
TOBACCO, RADON, AIR POLLUTION, OTHER RISK FACTORS – MONDAY, DECEMBER 5, 2016

P1.01-013 EMPHYSEMATOUS CHANGES AND PULMONARY FUNCTION FOR ASBESTOS-RELATED LUNG CANCER IN JAPAN
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Background: Smoking accelerates the incidence of asbestos-related lung cancer. We evaluated emphysematous changes by chest CT and pulmonary function for asbestos-related lung cancer in Japan. Methods: Two hundred and twenty-two patients of asbestos-related lung cancer were evaluated as age, gender, smoking index, histology, survival, therapy and occupational history including first asbestos exposed age, asbestos exposing terms and latency from the first asbestos exposure to lung cancer. Radiographic evaluation was done by chest CT using Goddard classification of emphysema. Pulmonary function test was done by spirometry and flow-volume curve. Results: Ages range from 49 to 92 years with a median of 75 years. Male occupied 97.7%. Non-smoker was only 13 patients and other 209 were smokers with Brinkman Index ranges from 45 to 3000 of a median of 900. For histology of lung cancer, 60.4% are adenocarcinoma and 22.4% of squamous cell carcinoma, 12.6% of small cell carcinoma, 2.6% of undifferentiated small cell carcinoma and 1.8 of large cell carcinoma and 2.6% of pleomorphic carcinoma. Eighty seven patients were operated and other 87 patients performed best supportive therapy. Median survival was 34 patients. Median survival was 2 years. Asbestos histology was 32 years and the latency of lung cancer was 50 years. Keywords: Asbestos, lung cancer, lung emphysema.
years. For Goddard score of emphysematous changes, 28% showed 0 point and 33% from 1-4 points and more than 21 points occupied only 4%, which means very low percentages of emphysematous changes for these asbestos-related lung cancer, nonetheless of high percentages of heavy smokers. For pulmonary function test, FEV1.0% is 70.5%±13.1% and %FEV1.0 is 85.6±22.2%. More than half patients are normal pulmonary function except more than 1,000 of Brinkman index or more than 15 points of Goddard score. From the classification of GOLD criteria, 54.1% are normal, stage 1 is 20.7%, stage 2 is 22.5% and stage 3 is 1.8% and stage 4 is only 0.9%. Conclusion: Almost all of asbestos-related lung cancer in Japan are heavy smoker, but 61% showed none or low grade of emphysematous changes by chest CT and only 2.7% had severe pulmonary dysfunction.

Keywords: Asbestos, smoking, emphysema lung cancer


P.01-014 THE ROLE OF HEREDITARY FACTOR, PROFESSION AND THE HABIT OF CIGARETTE SMOKING IN DEVELOPING LUNG CANCER
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Background: Lung cancer (LC) is the most common and deadliest cancer in the world. In the Republic of Macedonia, within the period 2002-2012, the LC took the first place according to the frequency of appearing in men, while it was on the fourth place in women. The number of the risk factors is great being connected with the occurrence of LC. The aim of this study was to analyze the role of genetic factor, professional exposure and the habit of cigarette smoking in occurrence of lung cancer. Methods: The research was conducted as a case-control study. It included 185 patients diseased of LC (investigated group-IG) and the same number of persons without malignant disease (control group-CG). In the study were included only interviewees with pathohistologically confirmed LC. Through calculating the risks of the Odds ratio (OR), the risk-factors, which had a role in occurrence of the disease, were quantified, while with the Confidence intervals (CI), the statistical significance for the error level less 0,05 (p) was defined. Results: According to the investigation results, malignant disease of two members in one family was found in 13,5% of the IG, 9,4% of the CG, respectively. Current smokers (CS) with present hereditary factor had almost 4 times (OR=3,95; 95%CI, 1,78-8,77) greater risk to become ill compared to the never smokers (NS) without hereditary factor. The risk was greater when the same would be compared to the NS with present hereditary factor (OR=8,76; 95%CI, 1,80-42,68). In the studied the professional exposition was present in 68,6% from IG, versus 67% in the CG. The highest risk for LC was found in transport workers (OR=2,50; 95%CI, 1,01-6,15) and automechanics (OR=2,31; 95%CI, 0,76-7,07). CS represented 67% of diseased individuals versus 40,5% of the CG. The risk for them to develop LC was 5,54 (95%CI, 3,0-10,23), times significantly greater compared to the NS. The risk for the disease was significantly greater in individuals who were smoking ≥20 years (y), ≥20cigarettes/day (1/1), compared to those, who, in the same time period, smoked <20c/day (OR=3,78;95%CI, 2,04-7,01). The risk to develop LC in former smokers (FS), who >20y smoked ≥20c/day was 2,40 (95%CI, 0,94-6,14), times greater compared to those, who smoked ≥20y, ≥20c/day. Conclusion: This disease developed twice more commonly in the examined individuals, exposed to professional carcinogens. The LC is multifactor disease for which development, besides smoking, as a main determinant, in mutual interaction are the genetic and other factors of the surrounding and the way of living.

Keywords: lung cancer, hereditary factor, cigarette smoking, occupation


P.01-015 POLYPHENOLS-RICH FRUIT EXTRACTS PREVENT TOBACCO SPECIFIC NITROSAMINE-INDUCED DNA DAMAGE IN LUNG EPITHELIAL CELLS
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Background: Diets rich in polyphenols are well-known to reduce lung cancer risk among high-risk populations. We analyzed the efficacy of polyphenols-rich Haskap (Lonicera caerulea L.) fruit extracts in preventing tobacco specific nitrosamine (TSNA)-induced DNA damage in BEAS-2B lung epithelial cells. Methods: Monomeric polyphenols of Haskap fruits were extracted in ethanol and water, and profiled. TSNA, 4-(methyltiosamine)-1-(3-pyridyl)-1-butanone (NNK) and 4-(acetoxethyl)-nitrösamin D (3-3-pyridyl)-1-butanone (NNKDAc) were used (at sub-lethal concentrations) independently to induce the carcinogenesis process in BEAS-2B cells. Cell viability assay was confirmed that the tested concentrations of Haskap extracts were not cytotoxic to BEAS-2B cells. Results: The Haskap extracts contain diversity of polyphenols including phenolic acids and flavonoids, however, cyanidin-3-glucuronide is the most predominant. Pre-treatment of cells with the Haskap extracts could significantly reduce the NNK- and NNKDAc-induced DNA double strand breaks, DNA fragmentation and intracellular reactive oxygen species, compared to non-treated cells. Immunocytochemistry for H2AX-phosphorylation (Serine 139, red) A) NNKOAc 100 μM, 3 h; B) Haskap ethanol extract (50 μg/mL, 3 h)+NNKOAc (100 μM, 3 h). DNA counter-staining was performed with 4,6-diamidino-2-phenylindole (blue).

Conclusion: The polyphenols-rich Haskap extracts could prevent TSNA-induced DNA damage in lung epithelial cells in vitro. Protective effects of Haskap polyphenols against DNA damage are being investigated in vivo using A/j mice.

Keywords: DNA damage, Haskap, Nitrosamine, BEAS-2B cells


P.01-016 AN INTERNATIONAL EPIDEMIOLOGICAL ANALYSIS OF YOUNG PATIENTS DIAGNOSED WITH NSCLC (ADUJOV - CLICAP)
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Background: Even though lung cancer remains a disease of a median age at diagnosis of 70y, a proportion of patients are diagnosed at 40y or younger. Patients diagnosed before the age of 40 are at a higher risk of having advanced disease, and may have different biologic characteristics. Methods: We conducted an international case-control study comparing the characteristics of patients younger than 40y. Our study groups the largest number of patients diagnosed before the age of 40 y and compares patients with NSCLC stage I-IIIA to patients diagnosed at older ages. Results: Almost all patients diagnosed before the age of 40 were never-smokers, whereas about 64% of patients diagnosed at older ages were current or former smokers. The majority of patients younger than 40y were diagnosed after age 70y, a proportion of patients are diagnosed at 40y or younger. Conclusion: Our study groups the largest population of patients less than 40y diagnosed with NSCLC. Methods: In this...
The French incidence. Incidence was 4.5 fold higher in prisons than in the general population among 30-40 years old peoples; 3.4 fold higher in 40-50 and 1.4 fold higher in 50-60 and 60+ years categories. Conclusion: There is a dramatic shift of lung cancer toward young peoples in prisons. However, presentation, management and prognosis are similar in prisoners compared to controls. These findings should justify a specific screening policy in that high-risk population.

Keywords: lung cancer, epidemiology, prison, case control study

P1.01-018 TOBACCO USE AND PERCEPTIONS ABOUT CESSATION TRAINING AMONG HEALTH PROFESSIONS STUDENTS: ESTIMATES BY COUNTRIES AND WHO REGIONS
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Background: Health professionals play an important role in cessation and prevention of tobacco use by providing a brief counseling or even a simple advice to their patients. Smoking habit among health professionals themselves may deter them from providing cessation advice and counseling to their patients. Using GHPSS data, we aim to provide updated global, regional, country-level estimates on prevalence tobacco use among medicine, dentistry, nursing and pharmacy students and describe their attitudes towards tobacco cessation training. Methods: The Global Health Professions Student Survey collects data on cigarette smoking and use of other tobacco products, training received to provide patient counselling on cessation techniques etc. We analysed country-wise aggregate data on current cigarette smoking’ (smoking cigarettes ≥1 days during the past 30 days), and ‘current use of tobacco products other than cigarettes’ (chewing tobacco, snuff, bidis, cigars, ≥1 days during the past 30 days), indicators of health professionals’ role’ and ‘cessation training’. We calculated aggregate rates for each World Health Organization regions using ‘metaprop’ command in Stata-11. Results: In 236 surveys from 2005 to 2011 from 70 (medical), 56 (dental), 56 (nursing) and 54 (pharmacy) countries 107,527 students (68,809, girls and 37,888 boys) were surveyed. Overall, in all courses smoking was highest in Europe (20%, medical to 40%, dental students) followed by the Americas (13%, pharmacy to 23%, dental students). Other tobacco use rates were higher in the eastern Mediterranean (10-23%) and Europe (7-13%) countries. Tobacco use among female students was lowest in Asian and African countries. In countries surveyed ≥70% of students agreed that medical professionals are role models and have a role in advising and information about smoking cessation to their patients and public. In the countries surveyed in all the regions, only about 9-2.3% of students (except 80% among dental students in the eastern Mediterranean) reported that they have received formal training in smoking cessation approaches. and ≥80% of all students agreed they should receive a formal cessation training. Conclusion: Health professions students ready to receive cessation training. Tobacco control experts should work with medical educators to discourage tobacco use among health professional students and implement integrated smoking cessation training into their medical curricula. Implications: Our results provide a global snapshot and regional estimates of tobacco use among health professions students and cessation training. Results highlight the need for cessation advice/advisance to health professions students currently using tobacco and the need for introducing cessation training particularly in developing Afro-Asian countries.

Keywords: Tobacco Use; Smoking Cessation; Health Professions Education; Epidemiology; Surveys

POSTER SESSION I - P1.01: EPIDEMIOLOGY, TOBACCO CONTROL AND CESSATION/PREVENTION
PROTECTIVE FACTORS, RISK REDUCTION, SMOKING CESSATION – MONDAY, DECEMBER 5, 2016

P1.01-017 THE DRAMATIC SHIFT OF LUNG CANCER TOWARD YOUNG IN PRISONS
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Background: Although prisoners could be at higher risk for lung cancers, very few studies focused on that particular population. In a previous cohort study (Carbonneau et al. Oncology 2013;85:370–377), we found an early onset of lung cancer in imprisoned patients. The aim of the CARCAN study was to assess epidemiological characteristics, management, prognosis and incidence of lung cancer among prisoners compared to general population. Methods: We designed a multi-centric observational case-control study. Cases were lung cancer diagnosed in prison in 3 penitentiary medical units (PMU) of France from 2005 to 2013 (Lyon/Marseille/Toulouse). Up to 3 controls were selected for each case from hospital databases. Controls were randomly matched to cases for center, sex, and year of diagnosis. Overall and age-specific cumulated incidences were calculated in the penitentiary area covered by the 3 participating PMU and in the French population using national statistics. Results: Overall, 170 controls and 72 cases met the inclusion criteria and were analyzed (male=90%). Median age at diagnosis was 52.9 (IQR=41.0) in prisoners and 64.3 (IQR=41.0) in controls (P<0.04). Most of prisoners were current smokers compared to controls (83% vs 53%, P<0.04). We did not find significant difference in histologic type or TNM stage at diagnosis between the two groups. Also, there was no significant difference in first-line treatment type between the two groups. Overall, there was no difference in the rate of patient undergoing supportive care only. Median time from first symptoms to first treatment was 3.3 months (2.7-3.9) in controls compared to 3.6 months (2.7-4.4) in prisoners (P=0.947). We found no significant difference in progression free and overall survival between the two groups. EGFR mutation (EGFRm) analysis was determined in 103 patients with 40 patients (38.8%) having an EGFRm. EMLA4-alk analysis was determined in 165 patients with 11 patients having a positive translocation (6.7%). The OS for the patients was 14.4 months (95% CI=11.2-17.5), PFS was 5.7 months (95% CI=4.9-6.5), and there was no significant difference according to histological subtype. OS for EGFRm (+) was 42 months (95% CI=30.8-54.0) and for EMLA4-alk it was 19.4 months (95% CI=14.8-24.0) (p=0.002); PFS for EGFRm (+) was 11.9 months (95% CI=6.3-17.5) and for EMLA4-alk it was 7.1 months (95% CI=5.3-8.9) (p=0.005). For alk (+) was 28.0 months (95% CI=15.4-40.6) and for alk (-) it was 10.6 months (95% CI=6.9-14.3) (p=0.065). Conclusion: NSCLC patients aged 40 years or less constitute a small but important proportion of patients with this diagnosis. Other risk factors may be involved in the pathogenesis of the disease in this population due to a low smoking history found. SNC metastasis at diagnosis seems to be more frequent in this population. EGFR mutation and EMLA-alk translocation frequency is higher than the frequency reported in the general population.

Keywords: NSCLC, 40 years or less, EGFR, young

Abstracts

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Background: In the lung screening population, the prevalence of lung cancer is typically a small percentage (2.3% (10/440) in our institution's program). A much more common, treatable, and potentially overlooked condition in the lung screened patient population is nicotine addiction. The National Lung Screening Trial contained 49% current smokers. A review of our lung cancer screening program showed 70.2% (309/440) of patients were active smokers at the time of lung screening. Methods: Our lung screening program is designed so that all scheduling would be done by a coordinator who is a Nurse Practitioner and a Certified Tobacco Treatment Specialist. A telephone call schedule the scan was done by the coordinator and basic tobacco cessation intervention was integrated into every call. Further follow up as face-to-face counseling was offered. We reviewed institutional data to determine what proportion of active smokers would agree to individualized counseling when it would be conveniently offered at the point of the scan, by the person coordinating the program. Results: Over a consecutive 26 month period, 440 patients underwent lung screening. The majority of patients (70.2, 309/440) were actively smoking. Telephone intervention reached 100% (309/309).

The telephone intervention consisted of an Ask, Advise, Refer strategy which offered further resources including: a quitline referral, a weekly group counseling session referral, and an indepth personal counseling session which would be provided at the time and place of the screening scan. The same tobacco treatment specialist who provided telephone intervention, met face-to-face with 80.6% (249/309) of active smokers for in depth counseling and development of a cessation plan. Conclusion: Our lung screening program detected lung cancer in a minority of participants (2.3%, 10/440) but encountered nicotine addiction in the majority of participants (70.2%, 309/440). Positioning Certified Tobacco Treatment Specialists as coordinators of lung screening programs ensure that all participants receive at minimum a telephone intervention. The initial telephone intervention coinciding with scheduling the screening scan allowed a relationship to develop between the patient and the coordinator (who is tobacco cessation specialist). Most participants who were smoking (80.6%, 249/309) agreed to in depth counseling which was conveniently provided at the point of service with the screening scan. Without integration of the resources, few patients would have sought out cessation counseling. As lung screening will recur annually, this will provide longitudinal support. Further data about acceptance of counseling and data about long term cessation in a lung screening program will be gathered.

Keywords: Smoking, cancer, nuclear

P1.01-02 CHEMOPREVENTIVE EFFECT OF CATECHIN HYDRATES AGAINST BENZO(A)PYRENE INDUCED LUNG CARCINOGENESIS IN MICE: PLAUABLE ROLE OF ALDH1
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Background: Lung cancer is a devastating disease with a poor prognosis. Chemoprevention has came out as a very promising protective strategy against cancer and numerous natural compounds in diet have shown their curative potential on lung cancer. Catechin is mainly found in green tea and is being widely used because of its chemopreventive nature on lung cancer. The present study was designed to investigate the mechanism-based chemopreventive nature of catechin hydrate (CH) against B(a)P induced lung carcinogenesis in Swiss albino mice and possible role of aldehyde dehydrogenase 1 (ALDH1).

Methods: B(a)P was administered orally (50 mg/kg body weight) twice a week for four successive weeks to induce lung cancer in mice. CH was supplemented to mice at doses of 20 and 40 mg/kg b.wt. The body weight, lung weight, lactate dehydrogenase (LDH), lipid peroxidation (LPO), xanthine oxidase (XO), carcinomembryonic antigen (CEA), antioxidants armory activities (SOD, CAT, GPx, GR, GST and GSH) were estimated. Further, histopathological analysis of lung tissue and Immunohistochemistry analysis of ALDH1, VEGF, PCNA, GF, COX-2, caspase-3 and Bcl-2 were also carried out. Results: Administration of B(a)P resulted in increased XO, LPO, and CEA with subsequent decrease in activities of tissue anti-oxidant armory (SOD, CAT, QR, GPx, GR, GST and GSH) were estimated. Further, histopathological analysis of lung tissue and Immunohistopathology revealed that CH pre-treatment effectively regulated hyperproliferation, inflammation and apoptosis in lung of mice. Immunohistochemical analysis also revealed that CH pre-treatment showed significantly reduced in ALDH1 expression. Further, the antiproliferative effect of CH was confirmed by histopathological analysis. Conclusion: Overall, our findings suggest that catechin hydrate inhibits B(a)P-induced lung tumor formation by modulating hyperproliferation, inflammation, apoptosis and ALDH1 expression.

Keywords: Catechin hydrate, aldehyde dehydrogenase 1, carcinomembryonic antigen, chemoprevention

Abstracts

P1.01-021 THE IMPACT OF SMOKING STATUS ON OVERALL SURVIVAL IN A POPULATION-BASED NON-SMALL CELL LUNG CANCER (NSCLC) SURGICAL RESECTION COHORT
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Background: Surgical resection is the optimal treatment modality for NSCLC, while smoking has been shown to have a negative survival impact. We evaluated smoking's impact on overall survival within a population-based cohort of patients with surgically-resected NSCLC. Methods: We examined all patients who had a curative-intent NSCLC resection from 2009-2016 in 4 contiguous Dartmouth Hospital Referral Regions of the US. We compared patient and clinical characteristics among never, former (stopped ≥1 year prior), and active smokers using the Chi-square and ANOVA tests. Survival analyses were conducted with the Kaplan-Meier method and Cox Proportional Hazards models. Results: Of 2,202 patients, 206 (9%) were never, 846 (38%) were former, and 1,150 (52%) were active smokers. Significant demographic and clinical differences between cohorts included age, sex, race, insurance, comorbidities, pulmonary function, method of detection, ASA status, extent, primary site and length of resection, histology, and histologic grade (all p<0.05). Short-term post-operative mortality (at 30, 60, 90, 120 days) rates for never smokers were 1%, 2%, 4%, 4%, for active smokers, 4%, 6%, 7% and 8%, and for former smokers, 5%, 7%, 9%, and 11%, and differed significantly by smoking status (p=0.0539, p=0.0316, p=0.0187, p=0.0017). At 5 years, overall survival was 69% for never smokers, 55% for active, and 49% for former smokers (p=0.0002) (Figure 1). Controlling for age, sex, race, insurance, histologic grade, extent of resection, and length of surgery, and compared with never smokers, active smokers had 1.3 times (p=0.05) the hazard of death and former smokers had 1.4 times the hazard of death (p=0.04).

Conclusion: In this population-based cohort, smoking is negatively associated with post-operative mortality and long-term overall patient survival; although active smokers had better survival outcomes than former smokers.

Keywords: Non-small cell lung cancer, Surgical resection, survival, tobacco control and cessation

P1.01-022 SMOKING CESSATION RELATED TO LUNG RESECTION
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Background: The impact of smoking status on lung resection outcomes is not well established, and the role of smoking cessation among lung cancer patients undergoing surgery is not clearly defined. An analysis of a cohort of patients treated at a large urban academic medical center was conducted to determine the impact of smoking status on lung resection and whether smoking cessation is associated with improved outcomes.

Methods: A retrospective analysis was conducted of a cohort of patients with surgically-resected NSCLC. Results: Of 2,202 patients, 206 (9%) were never, 846 (38%) were former, and 1,150 (52%) were active smokers. Significant demographic and clinical differences between cohorts included age, sex, race, insurance, comorbidities, pulmonary function, method of detection, ASA status, extent, primary site and length of resection, histology, and histologic grade (all p<0.05). Short-term post-operative mortality (at 30, 60, 90, 120 days) rates for never smokers were 1%, 2%, 4%, 4%, for active smokers, 4%, 6%, 7% and 8%, and for former smokers, 5%, 7%, 9%, and 11%, and differed significantly by smoking status (p=0.0539, p=0.0316, p=0.0187, p=0.0017). At 5 years, overall survival was 69% for never smokers, 55% for active, and 49% for former smokers (p=0.0002) (Figure 1). Controlling for age, sex, race, insurance, histologic grade, extent of resection, and length of surgery, and compared with never smokers, active smokers had 1.3 times (p=0.05) the hazard of death and former smokers had 1.4 times the hazard of death (p=0.04).

Conclusion: In this population-based cohort, smoking is negatively associated with post-operative mortality and long-term overall patient survival; although active smokers had better survival outcomes than former smokers.

Keywords: Non-small cell lung cancer, Surgical resection, survival, tobacco control and cessation

POSTER SESSION 1 - P1.01: EPIDEMIOLOGY, TOBACCO CONTROL AND CESSATION/ PREVENTION
PROTECTIVE FACTORS, RISK REDUCTION, SMOKING CESSATION – MONDAY, DECEMBER 5, 2016
Background: Smoking cessation interventions are often ineffective, although negative health effects of smoking are well established. However, evidence suggests that diagnosis of a severe medical condition or a surgical intervention may force people to quit smoking without any counseling. Aim of the study was to determine the smoking cessation rate among patients undergoing lung resection and factors associated with perioperative smoking cessation. Methods: All lung resection patients in one thoracic surgery department in 6 years were included. A phone-interview was conducted with all accessible patients aged ≥16. Willcoxon rank-sum test, and chi-squared or Fisher exact test were used for statistical analysis. Results: In 6 years 970 patients were operated on; 406 (229 male, 177 female; mean age 56.4 ± range 16 to 85) years were available for the study. At the time of surgery 155 patients (38.2%) were non-smokers; 82 (20.2%) ex-smokers, and 163 (41.6%) current smokers. 56.3% of males and 22.6% of females were smokers (p<0.0001). 14 patients had lung cancer and 261 patients other causes for lung resection, with different smoking distribution in these 2 groups (p<0.0001). Sixty-nine patients (40.8%) quit smoking before the operation: 22 due to the newly diagnosed operation, and 24 for other reasons. Seventy-two patients (42.6%) did not smoke after hospital discharge including 66 (39.1%) also a year later. An additional 40 (23.7%) patients had tried to stop, and 57 (33.7%) continued smoking. The quit rate was higher among lung cancer patients versus others (uncorrected p=0.007), and patients operated through thoracotomy versus VATS (uncorrected p=0.0295); and was not influenced by gender or duration of smoking. Conclusion: Almost 40% of patients undergoing lung resection stopped smoking without special counseling, with very few restarting. Smoking cessation rate was higher among patients with lung cancer and patients operated through thoracotomy.

Keywords: Smoking Cessation, Thoracic Surgery

P1.01-032 SMOKING CESSATION BEFORE INITIATION OF CHEMOTHERAPY IN METASTATIC NON-SMALL LUNG CANCER: INFLUENCE ON PROGNOSIS

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Background: The association between cigarette smoking and lung cancer mortality is well known. Some studies have shown a decreased overall survival (OS) in early stage non-small cell carcinoma (NSCLC) patients that continue to smoke after diagnosis. It is documented that in patients with metastatic disease, continued smoking increases resistance to systemic therapies but the impact of smoking cessation during treatment on outcomes for these patients is not well defined. Objective: To evaluate the impact of smoking cessation, before initiation of chemotherapy (CT), on survival in advanced NSCLC. Methods: Patients referred to our centre, between January 2010 and June 2016, and diagnosed with metastatic NSCLC were analysed. Patients defined as smokers at diagnosis and treated with at least one cycle of chemotherapy were included. Clinical characteristics and survival outcome were reviewed and compared between patients who quit smoking before and after the initiation of chemotherapy. Results: A total of 113 patients were included (mean age 59±10 years; 89.4% (n=101)). The histological type more predominant was adenocarcinoma (70.8%) and the most common sites of metastasis were lung, bone and brain (35.4%, 23.9% and 23%, respectively). The majority of patients had performance status 1 and no weight loss at time of diagnosis (53.7% and 58.4%, respectively) and the comorbidity most prevalent was hypertension (19.5%). The average number of cigarettes smoked was 51±33pack-years and 81.4% of patients smoked >30pack-years. The most used CT regimen was platinum combined with pemetrexed (63.7%). Patients who quit smoking before CT showed a better median OS although not statistically significant (8 vs. 7 months; p=0.478). This was also seen in heavy smokers ≥30pack-years, with a median OS of 8 vs. 6.5 months (p=0.674). The multivariate analysis only showed an influence of type of CT on survival. Conclusion: Although not significant differences in OS between groups were observed in our sample, the median survival was better in patients that quit smoking before the initiation of CT, even in heavy smokers. Continued smoking after CT initiation is known to adversely affect treatment response and quality of life and efforts to encourage smoking cessation even among this population of patients should be made.

Keywords: advanced NSCLC, Smoking Cessation, chemotherapy, survival
farming, exposing to companies’ tactics and other tobacco control activities. The study results also revealed that in controlling tobacco supply and demand effectively, media has been assisting the government and anti-tobacco activities productively. Majority of the Key Informants opined spontaneously on tobacco control program publicly, organizational interference, and influence of other activities on media. They also emphasized role of media for activities of anti-tobacco organizations, awareness building actions, popularization of tobacco control law and its amendment. Conclusion: The study showed that mass media coverage of tobacco control issues is influencing the context of comprehensive tobacco control programs. To reduce tobacco consumption, along with strict enforcement efforts, media should be used to assist with the implementation of the tobacco control law. A sustained nationwide campaign to educate the masses against the dangers of smoking and smokeless tobacco is needed and media can play an important role in creating further awareness about the dangers associated with tobacco consumption.

Keywords: Mass Media and Tobacco, Tobacco control in Bangladesh, Role of Mass Media

P1.01-026 TOBACCO USE, AWARENESS AND CESSATION AMONG MALAYALI TRIBES, YELAGIRI HILLS, TAMIL NADU, INDIA
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Background: Health is a state of complete wellbeing free from any discomfort and pain. Despite remarkable worldwide progress in the field of diagnostic, curative and preventive medicine, still there are large populations of people living in isolation in natural and unpolluted surroundings far away from civilisation, maintaining their traditional values, customs, beliefs and myths. India has the second largest tribal population of the world next to the African countries. About half of the world’s autochthonous people live in India, thus making India home to many tribes who have an interesting and varied history of origins, customs and social practices. The present study was conducted to assess the tobacco use, awareness and its effect on health among Malayali tribes, Yelagiri Hills, Tamil Nadu, India. Methods: The inhabitants of the 14 villages of the Yelagiri hills, who have completed 18 years and residing for more than 15 years present on the day of examination and who were willing to participate in the study were included. Data was collected from a cross-sectional survey, using a Survey Proforma, clinical examination and a pre-tested questionnaire which included Demographic data, tobacco habits. An intra-oral examination was carried out by a single examiner to assess the Oral Health Status using WHO Oral Health Surveys – Basic Methods Proforma (1997). SPSS version15 was used for statistical analysis. Results: Showing that among 660 study population, 381(57.7%) had no formal education, 217(32.5%) had primary education, 59(8.9%) had secondary education and 23(3.5%) had higher education. 10.9% smoked cigarette, 65% chewed raw tobacco, 18% chewed Hans and 4.1% usedBidis. Results showed that among 660 study population, 28% had a combination of smoking and smokeless tobacco usage. The reason for practicing these habits were as a measure to combat the cold, relieving stress and body pain after work, and the lack of awareness of the hazards of the material used. Prevalence of oral mucosal lesions in the study population was due to tobacco usage and alcohol consumption and lack of awareness regarding the deleterious effects of the products used. Conclusion: From the results of this study it may be concluded that the Malayali tribes were characterized by a lack of awareness about oral health, deep rooted dental beliefs, high prevalence of tobacco use and limited access to health services.

Keywords: Malayali tribes, Tobacco usage, oral health status, WHO oral health proforma, Beliefs.

P1.01-027 INCREASED RISK OF LUNG CANCER AMONG WOMEN WITH SUPERFICIAL TCC: A POTENTIAL RISK COHORT FOR LUNG CANCER SCREENING
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Background: Screening for lung cancer is recommended among heavy current or former smokers at age 55-80. Transitional Cell Carcinoma of the Bladder (TCC) and lung cancer share same risk factors, however the existence of TCC is not indicated as a reason for screening for lung cancer. Patients with invasive TCC undergo full staging and therefore lung cancer is usually detected if it co-exists. However, in superficial TCC, lung evaluation is not routinely done and may be missed. Here, we have studied the incidence of lung cancer among low stage bladder cancer patients aiming to evaluate if this can be defined as a population at risk. Methods: Methods: The SEER (Statistics, Epidemiology and End Results) database was used to determine the incidence and standardized incidence ratio (SIR), and the average time to discovery of lung cancer in Patients with localized TCC of the bladder (AJCC 6 stages T1 through T4), in years 2000-2013, stratified by age and gender, and compare them to the SIR for all solid tumors. Results: Results: based on 89691 patients (F:M Ratio 1:3.3), the SIR for all solid tumors was 1.95 [95%CI: 1.87-2.04] for women and 1.87 [95%CI: 1.83-1.91] for men. The SIR for lung cancer in women was significantly higher, 2.40 [95%CI: 2.19-2.62], with significance persisting among all age groups ≥50y. The SIR for men was 1.81 [95%CI: 1.73-1.9], not significantly different from the risk for all solid tumors in any age group. The median latency period until discovery of lung cancer was 5.41, 3.54, 2.76 and 0.08 years in women, and 4.41, 3.59, 2.96 and 0.96 in men, for age groups 50-59, 60-69, 70-79 and 80+, respectively. Conclusion: Conclusion: Incidence of lung cancer is higher in localized TCC patients than among the general population, and among women it appears to be significantly higher than the general risk of solid tumors. Early stage TCC patients may therefore stand to gain from lung cancer screening, and should be considered as potential screening candidates.

Keywords: TCC, lung cancer, Bladder, Women

P1.01-028 HIGH RISK OLDER SMOKERS’ PERCEPTIONS, ATTITUDES AND BELIEFS ABOUT LUNG CANCER SCREENING
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Background: The US Preventive Services Task Force recommends that smokers aged 55-80 should be screened annually with low dose computed tomography (LDCT). Successful implementation of lung cancer screening depends on being able to reach high-risk individuals. This study identified demographic, smoking history, health risk perceptions, knowledge, and attitude factors of older smokers related to LDCT agreement. Using binary logistic regression we produced a predictive model of factors to explain LDCT agreement. Methods: As part of a larger cross-sectional study, we conducted a cross-sectional, national, online survey of 549 older adults. Descriptive statistics were used to explore demographic characteristics. Binary logistic regression analysis was used to test local and US-level predictors for LDCT agreement. Results: Almost 80% of the sample believed that a person who continues to smoke after the age of 40 has at least a 25% chance of developing lung cancer and if asked, 79.4% would agree to a LDCT. Using Chi Square analyses, nine variables that were significant at the 0.10 level were selected for inclusion in model development. Four of the independent variables made a unique statistically significant contribution to the model: Believes that early detection of lung cancer will result in a good prognosis; Perceives accuracy of LDCT; Believes that LDCT would decrease worry without encouraging continued smoking. Conclusion: Older smokers are aware of the risks of smoking, are interested in smoking cessation, and most are interested in and positive about LDCT. Cognitive aspects of participation in screening are key to increasing the uptake of lung cancer screening and smoking cessation among high-risk smokers.

Keywords: LDCT, Attitudes and Beliefs, Smoking Cessation, older smokers

P1.01-029 PERSONAL AND HOSPITAL FACTORS ASSOCIATED WITH LIMITED SURGICAL RESECTION, IN-HOSPITAL MORTALITY AND
COMPLICATIONS IN NEW YORK STATE
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Background: Lung cancer represents 13.4% of all newly diagnosed US cancers and 27.1% of all cancer deaths. Early stage lung cancer is generally treated with surgical resection. Many patient- and hospital-level factors influence the selection of appropriate surgical procedures and their outcome. We identified patient- and hospital-level characteristics influencing the type of lung cancer surgical approach utilized in New York State and assessed in-hospital complications and mortality. Methods: Patients were selected from the Statewide Planning and Research Cooperative System, SPARCS (1995-2012) based on ICD-9-CM codes of diagnosis (162 and 165) and procedures (32.0-32.9). Surgery was categorized into: limited resection (LR: 32.2-32.3), lobectomy (L: 32 A), and pneumonectomy (P: 32.5-32.8). Statistical analyses were performed in SAS v9.4 and ArcMap v10.3.1. Results: There were 36,460 patients (age 60-75 years); 56% underwent L, 37% LR, and 7% P. LR patients were more likely to be older (OR, 1.01, 95% CI (1.01-1.02)), female (OR, 1.10 [1.06-1.15]), Black (OR, 1.24 [1.15-1.34]), with comorbidities (OR, 1.10 [1.04-1.16]) than L patients. Opposite trends were observed among P patients, except for race. Over time, the odds of P decreased, while those of LR significantly increased (OR, 1.22 [1.16-1.29] for years 2007-2012 vs 1995-2000). Teaching hospitals were less likely to perform LR over L (ORadj 0.82 [0.75-0.88]), while in-hospital mortality was similar (ORadj 0.66 [0.62-0.69]), while in-hospital mortality was similar (ORadj 0.88). In-hospital complications were significantly less after LR than L or P.

Conclusion: There is a growing trend towards LR, which is still more likely to be performed in older patients with co-morbidities. In-hospital outcomes were better for LR performed in older patients with co-morbidities. In-hospital outcomes were better for LR than L or P.

Keywords: Limited Surgical Resection, In-hospital mortality, In-hospital complications, Personal and Hospital characteristics


P1.01-030 FACTORS ASSOCIATED WITH MARGIN POSITIVE RESECTIONS FOR NON-SMALL CELL LUNG CANCER (NSCLC) IN THE MID-SOUTH REGION OF THE US
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Background: Incomplete resection of NSCLC has a negative impact on survival. We evaluated risk factors associated with positive margins within a comparative observational population-based cohort study. Methods: We conducted a curative intent resection cohort from 2009-2016 from 4 contiguous Dartmouth Hospital Referral Regions in 3 US states. Statistical analyses were performed using univariate and multiple logistic regression models. Results: Among the 2,275 NSCLC-rectected patients, 52% were male, 78% white, 45% Medicare insured, and 36% privately insured, with a median age of 67 years. Factors associated with a higher margin positivity rate included male sex, large cell histology, undifferentiated tumor grade, neo-adjuvant therapy, clinical stage IIA and IIIB, bilobectomy extent of resection, patients with abnormal diffusing capacity of the lungs for carbon monoxide (DLCO), use of bronchoscopic biopsy for diagnosis greater than 1 day before surgery, left lung resection, and tumor size >7cm (all p<0.15, Table 1). American Society of Anesthesiologists (ASA) score, prior lung cancer, smoking status, Charlson score, FEV1, PET/CT, brain scan, bone scan, mediastinoscopy, blood transfusion, and hospital were not associated with positive margins in univariate analyses (all p>0.15). Controlling for sex, histology, tumor grade, tumor size, neo-adjuvant therapy, clinical stage, extent of resection, DLCO, pre-operative bronchoscopic biopsy, and primary resection site in the multiple variable analysis, sex (p=0.034), clinical stage (p<0.001), extent of resection (p=0.0461), DLCO (p=0.0431), and bronchoscopic biopsy (p=0.0029) were independently associated with risk for positive margins (Table 1).

Conclusion: This detailed evaluation in a large regional cohort indicates patient-level characteristics are associated with positive surgical resection margins. Our recently published evaluation of the National Cancer Database also identified institutional factors that impact the rates of positive margins. Patient-level, surgery-level, and institutional-level factors should be considered jointly to fully understand factors impacting margin positivity rates.

Table 1

<table>
<thead>
<tr>
<th>Characteristics and categories</th>
<th>Total Number of Patients</th>
<th>Marginal Positive Rate</th>
<th>Unadjusted P-value</th>
<th>Adjusted P-value</th>
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<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Female</td>
<td>1688</td>
<td>3.3%</td>
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<td>0.0013</td>
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<tr>
<td>Male</td>
<td>1190</td>
<td>6.6%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>&gt;65</td>
<td>2170</td>
<td>4.8%</td>
<td>0.0585</td>
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<tr>
<td>&lt;65</td>
<td>283</td>
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<tr>
<td>Clinical Stage</td>
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<td>Stage III, IV</td>
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<tr>
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<td>Para-lobectomy/my</td>
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<td>Bilobectomy/my</td>
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<tr>
<td>Segmentectomy/Wedge</td>
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Bronchoscopic Biopsy

<table>
<thead>
<tr>
<th>Bronchoscopic Biopsy</th>
<th>Total Number of Patients</th>
<th>Margin Positive Rate</th>
<th>Unadjusted P-value</th>
<th>Adjusted P-value</th>
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<td>480</td>
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<td>EBUS</td>
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<tr>
<td>EUS</td>
<td>7</td>
<td>0.0%</td>
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<tr>
<td>Other</td>
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<tr>
<td>None</td>
<td>1675</td>
<td>3.5%</td>
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</table>

Primary Resection Site

<table>
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<th>Primary Resection Site</th>
<th>Total Number of Patients</th>
<th>Margin Positive Rate</th>
<th>Unadjusted P-value</th>
<th>Adjusted P-value</th>
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<td>L/L</td>
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<td>LL/L</td>
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<tr>
<td>L/LL</td>
<td>197</td>
<td>11.2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RL/LL</td>
<td>192</td>
<td>5.4%</td>
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<td></td>
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<tr>
<td>RL/RL</td>
<td>128</td>
<td>6.3%</td>
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<tr>
<td>RL/RR</td>
<td>343</td>
<td>4.3%</td>
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<tr>
<td>Right Lung</td>
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Tumor Size

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<th>Mean, Median (IQR)</th>
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<td>3-5 cm</td>
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<tr>
<td>5-6 cm</td>
<td>16</td>
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<tr>
<td>&gt;6 cm</td>
<td>13</td>
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</table>

Keywords: Surgical resection, Non-small cell, Positive margins
P1.01-031 DOES MALIGNANT PLEURAL MESOTHELIOMA (MPM) BEHAVIOUR DIFFER AMONG DECADES?

Fatma Abou Elkassm1, Mohamed Rahomam1, Iman Abou El Khirm2
1Medical Oncology, National Cancer Institute, Cairo/Egypt, 2Surgical Oncology, National Cancer Institute, Cairo/Egypt

Background: MPM is extremely aggressive and has a long-latency period. Hence, detected at advanced stages resulting in an unfavorable prognosis (1-2years). However, MPM prognosis has been improving over the past few years with availability of better diagnostic and treatment regimens. We aim to compare clinico-pathologic characteristics of old-MPM cases referred to National Cancer Institute(NCI)- Cairo university between (2002-2003) and new MPM cases (2012-2015)

Methods: Retrospective review of MPM cases presented to NCI. Data regarding demographics, histology, symptoms and signs, tumor staging and CT-findings were obtained from all patients’ records. Pearson’s Chi(2) and Fisher’s Exact tests were used for statistical analysis. Results: 1) Old cohort (n=100): 100 patients were encountered. Median age was 46 years. Males were 59 of cases. 30% has PS1. Asbestos exposure was documented in 74 cases. 44 cases were smokers, 25 cases were industrial-workers. Family history was positive in 12 cases. Dyspnea was the presenting symptom in 92 cases, chest pain in 83% and tuberculous pleuritis in 2 cases, effusion in all cases, pleural thickening in 80%, tracheal shift to the opposite-side in 23%, 12 represented 41%. Epithelial subtype 46.6%. Pathological T2= 34%. 2) New cohort (n=194): 194 patients were encountered. Median age was 53 years. Males and females were nearly equally distributed. Epithelioid subtype was 63.4%. RT-sided lesions were evident in nearly two-thirds of the cases. Pleural thickening was nodular in 131 (69.7%) cases. Inter-lobar fissure was thickened in 29.4%. Mediastinal Pleura was affected in 37.1%. Nearly, half of our cases had effusion. Ossification & calcification were detected in 8 (4.1%) cases. Contraction of hemithorax was identified in 77 (39.7%) cases. Chest wall invasion (CWI) was present in 18 (9.3%) cases. Pulmonary nodules were detected in one-fifth of the cohort. Metastases were detected in 9 (4.6%) cases (Figure).

Conclusion: By comparing both groups, we found that more lymph node involvement(Ns), less metastasis(Ms),older median age,more females, more epithelial subtype, less pleural effusion presentation, more pleural thickening were detected in group 2 (new cases) reflecting better staging, metastasization& PET-CT), early detection, more incidence in females and better treatment modalities.

Keywords: comparison, mesothelioma, clinicopathological, decades

POSTER SESSION 1: P1.01: EPIDEMIOLOGY, TOBACCO CONTROL AND CESSATION/ PREVENTION - LUNG CANCER SCREENING, DIAGNOSIS – MONDAY, DECEMBER 5, 2016

P1.01-032 EMERGENCY DEPARTMENT VISITS BY LUNG CANCER PATIENTS IN KOREA

Dong Won Park, Gun Woo Koo, Tai Sun Park, Ji-Yong Moon, Sang-Heon Kim, Tae-Hyeong Kim, Dong Ho Shin, Ho Joo Yoon, Jang Won Sohn
Department of Internal Medicine, Hanyang University College of Medicine, Seoul/Korea, Republic of

Background: Although lung cancer patients frequently require emergency medical care due to acute unbearable symptoms and lifethreatening conditions, there are limited data on them at the emergency departments (ED). National Emergency Department Information System Database (NEDIS) collects information about ED visits in Korean population. We aimed to determine the frequency and main causes of emergency consultations and the predicting factors for hospital admissions and deaths. Methods: In this retrospective observational study, we reviewed all the cases of ED visit for six months, from July 2014 to December 2014, in three university hospitals: Hanyang University Hospital and Chung-Ang University Hospital in Seoul, and Chungbuk National University Hospital in Cheongju. By reviewing all the medical records including NEDIS database, we identified cases with lung cancer and performed descriptive statistics and logistic regressions analysis. Results: Of all 62,369 ED visits, there were 292 ED visit (0.5%) by 216 patients with lung cancer. Among them, 76.4% had only one ED visit in study period. The main reasons for consultation were respiratory symptoms (36.8%) and fatigue/alteration of the general state (12.7%), and pain (12.4%). ED visit leads to hospital admission in 76.9% and hospital death in 25.1% of lung cancer patients. In multivariate analysis, the main independent predictor factors of medicalization are diagnostic phase of lung cancer (odd ratio 9.3) and the transfer from another hospital (odd ratio 4.9). The palliative phase with best supportive care alone (odd ratio 5.2) and abnormal heart rate at the time of ED visit (odd ratio 2.4) are statistically associated with death during hospitalization. Conclusion: Our study shows that ED visit is a frequent but clinically important event for patients with lung cancer. We might consider certain risk factors indicating hospitalization and death in lung cancer patients visiting ED to improve delivery of quality cancer care.

Keywords: Emergency Departments, Hospitalization, Death, lung cancer

POSTER SESSION 1: P1.01: EPIDEMIOLOGY, TOBACCO CONTROL AND CESSATION/ PREVENTION - LUNG CANCER SCREENING, DIAGNOSIS – MONDAY, DECEMBER 5, 2016

P1.01-033 EGFR MUTATION AND ALK: ARE PATIENTS BEING ADEQUATELY TESTED IN BRAZIL?

Gilberto Lopes1, Maria Fernanda Simões1, Oddone Braghiroli1, Edna Prado1
1Núcleo de Oncologia Da Bahia, Salvador/Brazil, 2Close-Up International, São Paulo/Brazil

Background: Lung cancer is one of the most common malignancies in the world. In Brazil, it is estimated that 28,200 new cases will be diagnosed in 2016. This cancer affects more men and is usually caused by tobacco exposure. The most common histology is adenocarcinoma and many of these patients have driver mutations which help guide therapeutic choice. The aim of this study was to delineate the epidemiological profile of patients with NSCLC in Brazil and to evaluate the prevalence of testing for ALK translocations and EGFR mutations in patients in the public and private settings in Brazil. Methods: Observational, descriptive, retrospective, multicenter study involving 230 public and private institutions in Brazil. We obtained data from a commercial database with 1642 Non Small Cell Lung Cancer (NSCLC) patients treated in the country between January and December 2015. Variables analyzed: age, sex, smoking, presence of EGFR and ALK mutation. Results: Out of 1642 patients, 814 were treated in the public service (49.57%) and 828 in private services (50.42%). Most patients were men (58.28% vs. 41.71% female). The mean age at diagnosis was 61.8 years (median 62 years), 32.58% were former smokers, 31.12% current smokers, 19.48% never smoked and data were not available for 16.8% of subjects. Most patients had metastatic disease at diagnosis (65.04%), 23.20% had stage III, 9.31% stage II and 2.43% stage I. 68.57% had adenocarcinoma, 27.52% squamous cell cancers, 1.4% large cell and 2.67% had other histological types. Among the 534 patients with non-squamous histology treated in public settings, 244 patients were tested for EGFR (64,69%) and only and only 36 were tested for ALK (6,74%). In private services, of 656 patients with non-squamous subtypes, 454 were tested for EGFR (69,2%) and 77 for ALK (11,73%). Conclusion: Overall, testing for EGFR mutations in patients in the public and private settings in Brazil and to evaluate the prevalence of testing for ALK translocations and EGFR mutations in patients in the public and private settings in Brazil.

Keywords: PREVALENCE, lung cancer, EGFR, ALK

POSTER SESSION 1: P1.01: EPIDEMIOLOGY, TOBACCO CONTROL AND CESSATION/ PREVENTION - LUNG CANCER SCREENING, DIAGNOSIS – MONDAY, DECEMBER 5, 2016

P1.01-034 ECOG SCALE OF PERFORMANCE STATUS IN LUNG CANCER

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POSTER SESSION 1 - P1.01: EPIDEMIOLOGY, TOBACCO CONTROL AND CESSATION/PREVENTION
Prognostic Factors, Treatment – MONDAY, DECEMBER 5, 2016

P1.01-036 LUNG CANCER SCREENING PROGRAM IS COST EFFECTIVE IN FRENCH SETTING: A MODEL BASED STUDY

Christos Chouaid1, Juliette Vella-Boucoud1, Jean Claude Pairon1, Anne Dubureç1, Bruno Detournay1, Laurent Boyer1, Bruno Houssset2, Pascal Andujar2, Isabelle Monnet1

1Chest Department, Ge Oncoest Creteil, Creteil/France, 2Inserm U955, Ist, Creteil/France, 3Cemka, Bourg La Reine/Creteil/France, 4Inserm U955, Creteil/France

Background: The National Lung Screening Trial (NLST) showed that screening with low-dose computed tomography (CT) as compared with chest radiography reduced lung-cancer mortality. There is no data's on the feasibility and cost-effectiveness of CT lung cancer screening program in the French setting. Methods: We estimated mena life-years gained, costs and incremental cost-effectiveness ratio (ICER) for screening with low-dose CT compared to no screening. Estimations of life-years gained were based on the efficacy of NLST trial applied to the general French population using the same inclusion criteria's that NLST trial (age of 55 to 74 years with a minimum of 30 pack-years of smoking and no more than 15 years since quitting) adjusted to sex, age and smoking status. Costs were limited to direct costs from the payer's perspective. We also performed sensitivity analysis based on several assumptions of program efficacy. Results: The target population was 5,551,141 subjects. Compared with no screening, screening with low-dose CT over a period of 2 years, will have an additional cost of 941,978 €, will provide 52.4 additional year of life with a corresponding ICER of 17,969 € per year gained. Sensitivity analysis showed that this result is sensitive to program efficacy (number, stage and survival of lung cancer diagnosed by stage and pts to subjects compliance rate to the program. Conclusion: Cost effectiveness of CT lung cancer screening program in a French population using the same main inclusion criteria's and outcomes of NLST trial appears as acceptable from the french health system

Keywords: model study, lung cancer screening, cost effectiveness

POSTER SESSION 1 - P1.01: EPIDEMIOLOGY, TOBACCO CONTROL AND CESSATION/PREVENTION
Prognostic Factors, Treatment – MONDAY, DECEMBER 5, 2016

P1.01-037 BASELINE DEMOGRAPHICS AND COMORBIDITIES OF PATIENTS WITH ADVANCED NSCLC COMPARED TO THE GENERAL POPULATION FROM TWO REGIONS IN SWEDEN

Stephan Linden1, Ana Banos Hernandez2, Josefine Reding3, Jonas Nilsson4, Nahila Justo5, Jukka Montonen5, Patrice Verpillat6, 7

1Global Epidemiology, Boehringer Ingelheim, Ingelheim/Germany, 2Mapi Group, Stockholm/Sweden

Background: Lung cancer is the most commonly diagnosed cancer in men and the third most common in women. However, detailed analyses of patient morbidity diagnosed with advanced non-small cell lung cancer (NSCLC) in routine clinical care, compared to the general population, is limited. Methods: This non-interventional study is based on existing data from the population-based national Swedish Cancer Registry. All patients diagnosed with advanced NSCLC between 2006 and 2013 receiving care in the regions of Skåne and...
P1.01-038 PROGNOSIS VALUE OF BODY MASS INDEX (BMI) AND WEIGHT LOSS AT DIAGNOSIS IN PRIMARY LUNG CANCER: RESULTS OF KBP-2010-CPHG STUDY

Didier Debievre1, Hugues Morel2, Bruno Raynard2, Jean-Philippe Oster3, Aya Bizieux1, Antoine Lévy1, Jean-Pierre Mathieu1, Patrick Dumont4, Étienne Leroy-Tergem2, Bernard Asselain5, François Blanchon1, Michel Giroux1

1Service de Pneumologie, Groupe Hospitalier Régional Mulhouse Sud Alsace (Ghrmsa) - Hôpital Emile Muller, Mulhouse/France, 2Service de Pneumologie, Centre Hospitalier Régional, Orléans/France, 3Unité Transversale de Diététique Et de Nutrition, Institut Gustave-Roussy, Villejuif/France, 4Service de Pneumologie, Hôpitaux Civils de Colmar - Hôpital Pasteur, Colmar/France, 5Service de Pneumologie, Centre Hospitalier Départemental de La Roche-sur-Yon, La Roche-sur-Yon/Le Mans/France

Background: We studied the relationship between 1-year mortality and weight at diagnostic in 6,965 adult patients followed for primary lung cancer in 104 general hospitals. Methods: Patients were classified into 5 groups: Group 1, underweight with recent weight loss; Group 2, underweight without recent weight loss; Group 3, normal weight; Group 4, overweight; Group 5, obese. Kaplan-Meier method (1-year mortality) and Cox multivariate analysis (independent risk-factors) were used. Results: Respectively, 11%, 4%, 45%, 29%, and 12% of patients belonged to Groups 1, 2, 3, 4, and 5. One-year survival was lower in Group 1 (27% (20%-30%)) and higher in Group 4 (50% (48%-%52%)) or 5 (53% (50%-57%)) than in Group 2 (47% (41%-53%)) or 3 (43% (42%-45%)) (Fig. 1). As compared with normal weight, overweight was an independent protective factor. Independent protective risk factors are presented in Table 1. Interaction analyses showed that overweight was a significant independent protective factor for stage IIIA and IIIB cancer (HR=0.77 [0.6-0.99], p=0.0038, HR=0.75 [0.59-0.97], p=0.029, respectively).

P1.01-039 DOES DISTANCE BETWEEN CHEST AND SURGERY DEPARTMENTS IMPACT OUTCOME IN LUNG CANCER PATIENTS? RESULTS OF KBP-2010-CPHG STUDY

Didier Debievre1, Violaine Frappat1, Stéphanie Dehette2, Jacky Croquet3, Michel Carbonnelle4, Patricia Barre5, Daniel Coteurre6, François Goupill7, Olivier Molinier8, Michel Giroux9

1Service de Pneumologie, Groupe Hospitalier Régional Mulhouse Sud Alsace (Ghrmsa) - Hôpital Emile Muller, Mulhouse/France, 2Service de Pneumologie, Centre Hospitalier de Meaux, Meaux/France, 3Service de Pneumologie, Centre Hospitalier de Cahors, Cahors/France, 4Service de Pneumologie, Centre Hospitalier Jacques Cœur, Bourges/France, 5Service de Pneumologie, Centre Hospitalier de La Côte Basque, Bayonne/France, 6Service de Pneumologie, Centre Hospitalier de Chauny, Chauny/France, 7Service de Pneumologie, CH de Meulan-Le Mureaux, Meulan-Le Mureaux/France, 8Université de Paris-Sud Orsay, Paris/France, 9Service de Pneumologie, Centre Hospitalier de Meaux, Meaux/France

Background: We studied the impact of the distance between chest and thoracic surgery departments on the outcome of patients followed, for primary lung cancer diagnosed in 2010, in the chest department of 104 French general hospitals participating in KBP-2010-CPHG study. Methods: 6,083 patients with non-small-cell lung cancer (NSCLC) participated in this study. Univariate and multivariate analyses were performed to identify independent factors for surgery and 1-year mortality. Distance from the usual thoracic surgery department in 2010 was collected for each chest department and included in the model as a 4-class variable: 0 km (same hospital), 1-34 km, 35-79 km, and ≥80 km. Results: Overall, 23% of hospitals had a thoracic surgery
Keywords: non small cell lung cancer, thoracic surgery department, mortality, Surgery

Table 2- Mortality (multivariate analysis: adjusted hazard-ratios)

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<tr>
<th>Stages</th>
<th>HR</th>
<th>95% CI</th>
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<td>Continuous</td>
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<tr>
<td>Sex</td>
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<td>Women</td>
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<td>Stages</td>
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<td>I</td>
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<tr>
<td>II</td>
<td>1.01</td>
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<td>PS4</td>
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<td>[0.02-0.32]</td>
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Table 2- Mortality (multivariate analysis: adjusted hazard-ratios)

<table>
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<th>p</th>
</tr>
</thead>
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<td></td>
<td></td>
</tr>
<tr>
<td>1-34</td>
<td>1.02</td>
<td>[0.94-1.11]</td>
<td>0.661</td>
</tr>
<tr>
<td>35-79</td>
<td>1.00</td>
<td>[0.91-1.10]</td>
<td>0.985</td>
</tr>
<tr>
<td>&gt;80</td>
<td>1.01</td>
<td>[0.93-1.09]</td>
<td>0.887</td>
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<tr>
<td>Age (year)</td>
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</tr>
<tr>
<td>Continuous</td>
<td>1.01</td>
<td>[1.01-1.01]</td>
<td>&lt;0.001</td>
</tr>
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<td>[0.37-0.46]</td>
<td>&lt;0.001</td>
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<tr>
<td>IIIB</td>
<td>0.65</td>
<td>[0.58-0.72]</td>
<td>&lt;0.001</td>
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</tbody>
</table>

Keywords: SEER, epidemiology, NSCLC long-term survival

Conclusion: In 2010, the absence of an on-site thoracic surgery department did not impair outcome in NSCLC patients managed in the chest departments of French general hospitals.
are needed to identify patients likely to benefit. Converting digital medical images into high-dimensional data (‘Radiomics’) contains information that reflects underlying pathophysiology and that can be revealed via quantitative analyses. We extracted radiomic imaging features from baseline CT scans (prior to initiation of immunotherapy) and identified features that predict response to immunotherapy in NSCLC patients. This work is an initial test of the hypothesis that radiomic data may predict who will respond favorably and who will not. Methods: We curated a subset of data and images from 13 different institutional immunotherapy clinical trials. Patients with stage III/IV NSCLC and received PD-1, PD-L1, or doublet checkpoint inhibitors. All target nodules were identified on the CT scan prior scan to initiation of immunotherapy. RECIST guidelines 1.1 were used to measure patient response from baseline to last follow-up scan. Based on last follow-up, 43 patients had progressive disease (PD) and 28 patients with partial response (PR) or complete response (CR). Since we focused on extreme responses, stable disease (SD) patients were not included in the current analyses. We extracted 219 radiomic features including size, shape, location, and texture information from a total of 210 target nodules (lung, lymph nodes, or other). Backward-elimination analyses were utilized to generate parsimonious radiomic models associated with objective responses (PD vs. PR/CR) and post estimation computed performance statistics. Results: There were no significant differences for the patient characteristics between patients with PD vs. CR/PR. Analysis of the radiomic features for all target nodules to differentiate PD patients vs. PR/CR patients resulted in a final model containing 2 features that provided an AUROC of 0.64 (95% CI 0.56–0.72). When we analyzed features for only lung target nodules, we identified a final model with 4 features that produced an AUROC of 0.79 (95% CI 0.68–0.89). When we analyzed the imaging features of all lymph node target nodules, we found that a final model with 1 feature yielded an AUROC of 0.67 (95% CI 0.51–0.82). Conclusion: Radiomic features of lung target nodules have better performance statistics for predicting response to immune therapies compared to target nodules from other organ sites. With this model, cutoffs can be chosen to rule-in or rule-out patients with high confidence. Change feature analyses following therapy is underway.

Keywords: Imaging Epidemiology, Radiomics, Immunotherapy, Quantitative imaging

P1.01-042 MOLECULAR EPIGENETIC ANALYSIS OF IPF PATIENTS WITH NO GENETIC MUTATIONS: A NEW BIOLOGIC EXPRESSION

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1Cancer Epidemiology, H Lee Moffitt Cancer Center and Research Institute, Tampa/FL/United States of America, 2Astrazeneca, Gaithersburg/MD/United States of America, 3Astrazeneca, Cheshire/United Kingdom, 4Astrazeneca, Hertfordshire/United Kingdom

Background: In the United States, lung cancer occurs in about 225,000 patients and causes over 158,000 deaths annually. Due to a shift in smoking patterns between the genders that started decades ago, the incidence of lung cancers appeared to have shifted accordingly. Thus, we analyzed our institutional data as described below. Methods: This is a retrospective study that compares two populations of lung cancer patients in two different five-year periods a decade apart: one from 1996 to 2000 consisting of 1355 lung cancer patients and the other from 2011 to 2015 consisting of 2220 lung cancer patients from our institutional tumor registry data. We included lung cancers that have been associated with smoking such as adenocarcinoma, squamous cell carcinoma, and small cell lung cancer. The two populations were compared in category of gender, race and marital status were also included to examine any major population shifts during these time periods. Crude survival in the 2-year follow-up period was also examined. The results were analyzed using Excel as well as Matlab. This project is IRB approved. Results: From 1996 to 2000, the percentage of male population with lung cancer associated with smoking was 63%. This number decreased significantly to 51% in the period 2011-2015 (p-value < 0.00001). The percentage of African American patients in 1996-2000 was 14% and decreased to 11% in 2011-2015 (p-value 0.00039). The number of divorced patients increased from 8.1% to 11% (p-value 0.0025). The number of widowed patients decreased from 12.3% to 9.8% (p-value 0.00066). For patients with stage IV lung cancer diagnosed from 1996 to 1998, the crude survival rate at 2-year follow up was 17%, which increased to 29% in patients diagnosed from 2011 to 2013 (p-value < 0.00001). Conclusion: Our results demonstrate that the proportionate incidence of lung cancer in males has decreased significantly from the late 90s to the early 2010s. The change in race and marital status, while statistically significant, is less dramatic. The proportion of African American population has also decreased significantly. The crude survival rate at 2 year follow up for those with stage IV lung cancer significantly increased. While this could, in part, be due to stage migration, a real prolongation due to improvements in systemic therapy is likely. More attention should be drawn to the fact that nearly twice as many women die from lung cancer compared to breast cancer, for a more proportionate support of research efforts.

Keywords: lung cancer, gender distribution

P1.01-044 ACCELEROMETER-DETERMINED PHYSICAL ACTIVITY AND SEDENTARY TIME AMONG LUNG CANCER SURVIVORS

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1Oncology, University of Calgary, Calgary/AB/Canada, 2University of Calgary and
Background: Physical activity is an effective way to positively influence health outcomes among cancer survivors. Few studies have examined physical activity and sedentary behaviour among lung cancer survivors. Further, these studies have used self-report measures of physical activity, which may bias results (e.g., overestimation) and lead to incorrect conclusions. Only one study to date has reported on objectively-assessed sedentary behaviour among lung cancer survivors. The primary aim of this currently ongoing study is to determine the prevalence of objectively-assessed physical activity and sedentary time among lung cancer survivors. Methods: Lung cancer survivors in Southern Alberta diagnosed between 1999 and 2016 are currently being recruited to participate. Eligibility criteria include: confirmed non-small cell lung cancer, completed treatment, and not living in hospice/palliative care. Consenting participants wear an Actigraph GT3X+ accelerometer on their hip for seven days. Time spent sedentary, in light and in moderate-to-vigorous intensity physical activity are derived from the accelerometer data and processed using 60-second epochs. Physical activity and sedentary behaviour accumulated in 10 minute and 30 minute continuous bouts will be examined. Results: Recruitment began in June, 2016. A total of 660 survivors were invited and 437 agreed to participate. Of the 374 survivors that did not respond, most indicated they were not interested (n=115). Others denied having lung cancer (n=6) or had invalid contact information (n=27). Six were deceased. Currently the response rate is 18.2%. Of the 113 that consented, eight were lost to follow-up (n=7) and P (23.87±36.56 km; p < 0.001). At multivariable analysis, P-H was positively associated with teaching hospitals (β: 1.57, p < 0.001), and inversely associated with female gender (β: -3.37, p < 0.001), private insurance (β: -0.81, p < 0.001), and mortality (β: -1.05, p = 0.08). Similar associations were found in the L subgroup; among LR patients there was no statistically significant association between P-H and female gender.

Conclusion: Significant differences exist in P-H and patient/hospital characteristics, which may affect type of surgery and outcome. P-H should be incorporated to improve health disparities in accessing surgical care.

Keywords: Surgery, lung cancer, Patient-Hospital Distance

P1.01-045 PATIENT TO HOSPITAL DISTANCE IN ACCESS TO CARE AND LUNG CANCER SURGICAL TREATMENT
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Background: Lung cancer represents 13.4% of all newly diagnosed US cancers and 27.1% of all cancer deaths. Health disparities exist in accessing proper care and receiving surgical treatment. We examined the role of Patient to Hospital distance (P-H) in access to care. Methods: Patients were selected from the New York Statewide Planning and Research Cooperative System (1995-2012) based on ICD-9-CM diagnosis (162 and 165) and procedures (22.0-22.91). Surgeries were categorized into: limited resection (LR: 22.32.3), lobectomy (L: 22.32.4), and pneumonectomy (P: 22.35.2.6). Distance calculations (ArcMap 10.3.1) and linear regressions (SAS v9.4) were performed to determine the factors influencing P-H. Results: There were 36,460 patients (age 60-75 years); 56% underwent L, 37% LR, and 7% P; 95% of patients underwent surgery from the NSCLC surgical outcome registry, which included 5060 patients who underwent lung resection surgeries from 17 tertiary hospitals nationwide in 2013-2014. Baseline data, surgical treatment pattern parameters, pathology, number of lymph nodes dissected, and total hospital costs. Heterogeneity of quantitative data was analyzed using Kruskal-Wallis test. Results: Among the 5060 patient, the mean age was 59.7, while 3204 were male. Mean pre-op forced expiratory volume in 1 second (FEV1) was 2.23L (P<0.01), FEV1/FVC was 81.8% (P<0.01). 64.6% patients combined with at least one comorbidity. The average diameter of the tumor was 3.28cm (P<0.01). The post-operative pathology confirmed 59.8% as adenocarcinoma while 30.2% as squamous carcinoma. Based on the data submitted by different centers, 88.4% (mean, 0.98) patients were confirmed as stage III patients received adjuvant therapy before surgery (P<0.01). The rate of minimally invasive surgery was 48.1% (mean, 8.1 to 94.7%) in different regions (P<0.01). The number of stations of lymph nodes harvested was 5.8 (mean, 4.3 to 7.4) (P<0.05). Mean hospital cost was $5070 (mean, 43051 to 69686) RMB (P<0.01).

Conclusion: Significant differences exist in P-H and patient/hospital characteristics, which may affect type of surgery and outcome. P-H should be incorporated to improve health disparities in accessing surgical care.

Keywords: Surgery, lung cancer, Patient-Hospital Distance
8 4.8 42206 8.3 98.6 265

Conclusion: The heterogeneity of surgical treatment is quite huge in different centers of China. The baseline status before surgery, pre-operative therapy strategy, surgical technique, and health economic data submitted to the registry showed imbalanced development of NSCLC surgical treatment in different regions of China.

Keywords: registry study, health economic, surgical treatment pattern, Chinese NSCLC surgical outcome

POSTER SESSION 1: P1.01 EPIDEMIOLOGY, TOBACCO CONTROL AND CESSATION/ PREVENTION
PROGNOSTIC FACTORS, TREATMENT – MONDAY, DECEMBER 5, 2016

P1.01-047 CLINICAL PRESENTATION AND OUTCOME OF NEUROENDOCRINE LUNG TUMORS IN A BRAZILIAN COHORT FROM 2000 TO 2016

Marcelo Corassa, Vladimir Cordeiro De Lima, Aldo Dettino, Diego Silva, Thiago De Oliveira, Helano Freitas
Medical Oncology, A.C. Camargo Cancer Center, Sao Paulo/Brazil

Background: Neuroendocrine lung tumors (NET) are rare and heterogeneous neoplasms. Typical carcinoids (TC) and atypical carcinoids (AC) have better prognosis and their treatment is mainly focused on surgery. Large cell neuroendocrine carcinomas (LCNLC) are commonly widespread at diagnosis. Here we present clinical characteristics and outcome of patients with TC, AC and LCNLC treated at ACCCC from 2000 to 2016. Demographic variables included individual data, diagnostic and treatment patterns. Data was collected and processed to obtain outcomes and survival information. It was intended to obtain not only epidemiologic characteristics, but also to determine and confirm selected variables as prognostic. Results: Main demographic results are described in the Table below:

<table>
<thead>
<tr>
<th>VARIABLES</th>
<th>TC</th>
<th>AC</th>
<th>TOTAL</th>
</tr>
</thead>
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<tr>
<td>NUMBER OF PATIENTS</td>
<td>64(56.1%)</td>
<td>24(21.1%)</td>
<td>88(100%)</td>
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<tr>
<td>SEX</td>
<td></td>
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<tr>
<td>MALE</td>
<td>53.1%</td>
<td>41.7%</td>
<td>45.5%</td>
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<tr>
<td>FEMALE</td>
<td>46.9%</td>
<td>58.3%</td>
<td>54.5%</td>
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<tr>
<td>MEDIAN AGE YEARS</td>
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<td>53.74</td>
<td>57.48</td>
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<tr>
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<tr>
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<td>4.8%</td>
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<td>8.5%</td>
</tr>
<tr>
<td>III</td>
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<td>4.9%</td>
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<td>IV</td>
<td>4.8%</td>
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<td>≥1</td>
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<td>79.2%</td>
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<tr>
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<td>7.8%</td>
<td>20.8%</td>
<td>11.4%</td>
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For the entire population, median progression free survival (mPFS) was 158.5 months. mPFS was not reached (NR) for TC and AC, with 5-year PFS 81% for TC and 84% for AC and 10-year PFS 60% for TC and 59% for AC, no Statistical Significance (SS) was found between TC and AC in mPFS (p=0.549). mPFS was worst, with SS, for age ≥65 years (158.5x61.5 months; p=0.018), staging ≥2 (NRx75.7 months; p=0.027), ECOG ≥1 (158.5x35.2 months; p=0.001), node positive disease (N0xN1: NRx33.9; p=0.001). Same tendencies were observed for TC, also with SS, but not for AC. Median overall survival (mOS) retained the same tendency: 5-year OS was 74% for TC and 55% for AC and 10-year OS was 74% for TC and 47% for AC. mOS was not reached. Age ≥65 years (p=0.001), ECOG ≥1 (p=0.001) and staging ≥2 (p=0.001) also were predictable for worst mOS. Conclusion: This study demonstrates an epidemiologic descriptive outlook of neuroendocrine LCN in a Brazilian population. Older age, worst performance and higher staging were prognostic for poor outcomes in survival.

Keywords: Atypical Carcinoid, epidemiology, Neuroendocrine Lung Cancer, Typical Carcinoid

POSTER SESSION 1: P1.01 EPIDEMIOLOGY, TOBACCO CONTROL AND CESSATION/ PREVENTION
PROGNOSTIC FACTORS, TREATMENT – MONDAY, DECEMBER 5, 2016

P1.01-048 FACTORS CONTRIBUTING DELAYS DURING MANAGEMENT OF LUNG CANCER: A STUDY FROM TERTIARY LEVEL HOSPITAL IN NEPAL

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Background: Lung cancer is the leading cause of cancer related morbidity and mortality in both the sexes in Nepal. It accounts for 15.4 % of total cancer as per hospital based Cancer Registry in Nepal. Majority of patients are diagnosed and treated at advanced stage. This can be partly contributed to long lag period between the onset of symptoms and the initiation of cancer treatment. This study tries to evaluate the factor contributing delays in various steps in lung cancer diagnosis and treatment. Methods: This retrospective cross-sectional observational study was conducted at Department of Clinical Oncology, Bir Hospital, National Academy of Medical Sciences (NAMS), Nepal. We reviewed the record of the all registered, histologically diagnosed lung cancer patient during the year 2012 and 2013 Results: A total of 123 patient’s were diagnosed as Lung cancer and their records were evaluated. Out of these 123 patients, 60% of the cases were males. The mean age was 63.93 years with the youngest being 35 and the eldest was 83 years. Significant number of patient was in stage III (50%) and IV (33%). About 89% of the patients were smokers. Non-small cell lung cancer (NSCLC) accounted 83% and small cell lung cancer was (SCLC) 17%. A total of 17% (21) of patient were on empirical Anti-tubercular treatment (ATT) since the onset of current symptoms. While analyzing delay with independent T test showed mean delay of 25.01 days (+/- SD 6.17) in patient without ATT and with ATT delay was 57.09 days (+/- SD 8.05) (p=0.01). Thirty five percentage (43) of patient received treatment within 1 month from the first hospital visit, 28% (34) within two months and 37%(45) within 3-4 months of the first hospital visit. The delay in specialist visit was shorter in advanced cancer and small cell cancer may be because of the acute presenting symptoms. Conclusion: Various factors contributing for the delays are lag time from symptom onset to first visit with primary physician, delay due to investigation and symptomatic treatment under primary physician care, delay further aggravated by empirical but inappropriate ATT, further delay due to diagnostic procedure to establish the cancer diagnosis. Thus proper and timely referral to the specialist from primary physician will reduce these delays and help to avoid situation where curable disease become incurable and significantly alters the prognosis.

Keywords: Anti-tubercular treatment, Lung Cancer, Treatment delay,

POSTER SESSION 1: P1.01 EPIDEMIOLOGY, TOBACCO CONTROL AND CESSATION/ PREVENTION
PROGNOSTIC FACTORS, TREATMENT – MONDAY, DECEMBER 5, 2016

P1.01-049 PREDICTORS OF HIGH GRADE TOXICITY OF CHEMOTHERAPY AMONG MALIGNANT PLEURAL MESOTHELIOMA PATIENTS

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Background: Malignant pleural mesothelioma is an aggressive thoracic malignancy associated with exposure to asbestos, and its incidence is
anticipated to increase during the first half of this century. Chemotherapy is the mainstay of treatment, yet sufficiently robust evidence to substantiate the current standard of care has emerged only in the past 5 years. Methods: A retrospective cohort study of 100 MPM patients referred to NCI, Cairo University in 3 years. Detailed data, Pearson's Chi (2) square and Logistic regression model were used for statistical analysis. Results: We found a statistical significant relation between age (0.005), male gender (0.002), endemic area residence (0.001), industrial workers (0.018), duration of exposure (0.06), smokers (0.009), Simian virus (0.019), PS3 (0.001), RBp (0.001), PS (0.016) and development of high grade toxicity of platinum based chemotherapy. Median age = 66 years, only 17% of cases developed high grade toxicity complications of platinum based chemotherapy. Males were 59% of cases. PS, residence, smoking, occupation, history of asbestos exposure, family history, simian virus, PS3, RBp, dyspepsia, chest pain, cough, expectoration, haemoptysis, weight loss, fatigue, metastatic symptoms, chronic lung infection, Tuberculosis pleuritic, effusion, pleural thickening, Tracheal shift, TNM staging, surgical operations, pathological staging, radiotherapy, cause of death and chemotherapy toxicity are assessed in our patients. Conclusion: Many factors predict high grade chemotherapy toxicity. So, search for target therapy and immunotherapy instead of chemotherapy in this selected group can improve both quality of life and response rate.

Poster Session 1 - P1.01: Epidemiology, Tobacco Control and Cessation/Prevention

Prognostic Factors, Treatment - Monday, December 5, 2016

P1.01-050 OVERALL SURVIVAL IN ADVANCED LUNG CANCER PATIENTS TREATED AT ONCOSALUD-AUNA

Alfredo Aguilar1, Claudio Flores2, Luis Mas1, José María Gutierrez1, Luis Pinillos1, Carlos Vallesjos1
1Department of Medical Oncology, Oncosalud - Auna, Lima/Peru, 2Dirección Científica y Académica, Oncosalud - Auna, Lima/Peru, 3Radiología - Auna, Lima/Peru

Background: Lung cancer still remains as the principal death cause in many regions around the world. Unfortunately, between 60-70% of patients are diagnosed with advanced disease (clinical stage IIIB-IV). We report the overall survival of advanced lung cancer in patients treated at private institution (Oncosalud – AUNA). Methods: We analyzed data of 75 patients with advanced lung cancer and treated at Oncosalud-AUNA between 2013-2014. Overall survival was determined using Kaplan-Meier method and survival curves comparison were performed using logrank test. Results: The median age was 70 years (range: 39-91) and 69% of patients were women. In patients with clinical stage IV, the metastatic sites were generally brain (28%), osseous (18%), cervical and supraclavicular (14%). The 66.7% of patients received chemotherapy with/without radiotherapy, 9% radiotherapy only and 24% non-treatment. In patients previously treated with chemotherapy, 52% received targeted therapy. The 77% of patients had the follow-up median of survivors was 23 months (CI95%: 17-29), survival median was 9.6 months (CI95%: 5.6-13.5) and 1 and 2 years survival rate were 38% and 23%, respectively. The survival rate at1 and 2 years in those receiving targeted therapy were 65% and 43%, and those who did not receive were 35% and 10%. The overall survival present a difference according to ECOG scale (p = 0.015) and CYFRA 21.1 (p = 0.004). Conclusion: Overall survival for our patients is similar to other series. Patients under ECOG scale 2 and CYFRA 21.1 ≥ 3.3ng/ml had a relatively better prognostic.

Keywords: Lung cancer, overall survival

Poster Session 1 - P1.01: Epidemiology, Tobacco Control and Cessation/Prevention

Prognostic Factors, Treatment - Monday, December 5, 2016

P1.01-051 PREDICTOR VARIABLES TO ECOG SCALE OF PERFORMANCE STATUS IN LUNG CANCER AT A DEVELOPING COUNTRY IN LATIN AMERICA

Silvia Josefina Ayala Leon1, Miguel Antonio Agüero Pino2, Cinthia Viviana Gauna Colás3, Miguel Ayala León2
1Pulmonary and Thoracic Oncology Unit and Laboratory of Personalized Medicine, Instituto Nacional de Cancerología, Mexico City/Mexico, 2Public Health, Faculty of Medicine, National Autonomous University of Mexico, Mexico City/Mexico, 3National Cancer Institute Prof Manuel Riveros, Capitana/Paraguay, Mexico DF/Mexico

Background: We need to understand the living quality in our population, so we review performance status focus on ECOG 3, 4,5 that includes a concept of capable of limited self-care, because this increases expenses at families and health system. We need to understand the variables that increases risk of higher ECOG values. Methods: Between January 2004 and December 2013, all patients diagnosed with a pathology of SCLC and NSCLC at National Institute of Oncology at Paraguay were analyzed retrospectively. ECOG performance status was recorded and SCLC and NSCLC were used to analyze logistic Binary regression Results: We studied 478 subjects. At age mean 60,40 [95% CI 59,45 to 61,34] years and ECOG performance status mean 2,13 [95% CI 2,06 to 2,20] points. Bivariate correlations show no relation with age, gender, living place, work, smoking, alcohol consumption, histopathology of lung cancer only with motive of consultation and clinical severity. In our model of predicting a ECOG 3 to 5 adding first motive of consultation show a Nagelkerke R2 0.14, Hosmer y Lemeshow P 0.09. Adding to the model clinical severity Nagelkerke R2 0.07 Hosmer y Lemeshow P 1.0. Variables in our predicting model show at clinical severity IIb stage OR 6.62 [95% CI 13.33 to 38.52 P = 0.035], clinical severity IIA stage OR 3.85 [95% CI 13.18 to 12.51 P = 0.025], clinical severity IIB stage OR 4.49 [95% CI 13.87 to 7.08 P = 0.001]. At limited-stage SCLC clinical severity OR 10.12 [95% CI 1.18 to 54.34 P = 0.007]. At first motive of consultation chest pain OR: 3.13 [95% CI 1.38 to 7.11 P = 0.006]. Cough OR: 2.30 [95% CI 1.11 to 4.76 P = 0.024]. Palpable Tumoral mass OR: 8.35 [95% CI 1.65 to 42.07 P = 0.010]. Conclusion: Regardless our expectations about relation of disability of patient with lung cancer about place of living, work, gender, age these variables show no relation with ECOG at 3 to 5. In our review we found a prediction model with clinical severity adding 7% to prognostic of limited self-care and by adding to the model first motive of consultation a 14% of prognostic of worst ECOG status. If first consultation motive is chest pain, cough or palpable tumoral mass, this are strongly related with worst ECOG values. As a conclusion most of our patients are diagnostic in advance clinical stages with a bad performance status which will limited our options to treatment. All of these can be related with a late consultation or a late detection of the disease.

Keywords: Lung neoplasm, quality of life, Neoplasm Staging

Poster Session 1 - P1.01: Epidemiology, Tobacco Control and Cessation/Prevention

Descriptive Epidemiology – Monday, December 5, 2016

P1.01-052 LUNG CANCER MORTALITY IN MEXICO, 1990-2014

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1Public Health, Faculty of Medicine, National Autonomous University of Mexico, Mexico City/Mexico, 2Thoracic Oncology Unit and Laboratory of Personalized Medicine, Instituto Nacional de Cancerología, Mexico City/Mexico

Background: Mortality from lung cancer ranks first in men and third in women in Mexico. We aim to assess the mortality rate from lung cancer in the Mexican population during the period from 1990 through 2014. Methods: In this longitudinal study we analyzed the mortality data from Mexican population, which was obtained from the Population and Housing Census. Deaths were taken from the mortality database of the Ministry of Health of Mexico. The degree of marginalization of the population was made based on the marginality index established by the National Population Council, it includes five categories of marginalization: Very low, low, medium, high and very high. The 33 states of the Mexican Republic are divided into these categories, approximately being six to seven in each. Finally, the annual percentage change was calculated. Results: During the study period a decrease we observed a decrease in the lung cancer mortality rate adjusted for age and gender. Thus, the rate in 1990 was higher (110 deaths per 100,000 population), which decreased to 90 per 100,000 in 2014, representing a decrease of more than 15%. In relation to gender we observed a decrease in the mortality rate for both genders. In addition, the mortality rate in women was three times lower from that among men throughout the whole period of study. Nonetheless, we observed a slight increasing trend for women in the last years. Regarding the marginalization index we observed that the highest mortality rates occur in the states that comprise the categories with low and very low marginalization. Moreover, decline in mortality was also observed in those categories, unlike the categories of high and very high marginalization, where a slightly increase was observed during the period of study. Conclusion: Mortality from lung cancer has declined during the studied period, a situation that may be due to various situations such as diagnosis at earlier clinical stages or treatments more effectively, or under registry of mortality in the states that make up the categories with high or very high marginalization. Such situations must be studied in greater depth to identify the causes for the decline in mortality from lung cancer.

Keywords: Degree of marginalization, Mexico, lung cancer, Mortality rate
Background: The objective of this study was to describe the trends of histology and age of patients with non-small cell lung cancer (NSCLC) treated with lung resection according to gender. The histology of lung cancer is changing in developed countries and there is still little information available for developing countries. Methods: Retrospective analysis of all patients (n = 1030) with resected NSCLC between 1986 and 2015 in a university hospital of Southern Brazil. Differences in histology, stage and type of surgery were analyzed by sex and period (1986-1995, 1996-2005 and 2006-2015). Results: Most patients were males (64.5%), main histologic types were adenocarcinoma (44.5%) and squamous cell carcinoma (40.6%). Mean age at surgery was 56.5 years for women and 58.9 years for men in first period, and 62.2 for women and 64.6 for men in the last period (p<0.001), suggesting that it was approximately 2.4 years higher for men (p<0.001), in spite of the period. The proportion of histologic types were different by gender (p<0.001), showing that overall squamous cells carcinoma was more frequent in men (46.9%) than in women (29%), and the opposite occurred for adenocarcinoma (40.4% versus 51.8% for men and women, respectively). Analyses by period showed squamous cells carcinoma declined from around 38.9% in the first period to 23.2% in 2005-2015 for men, virtually equaling the proportion of adenocarcinoma in the last period. The proportion of adenocarcinoma in women increased from 11.9% in the first period to 24% in the last period. Considering all NSCLC patients, females with adenocarcinoma represented 11.9% in the first and 24% in the last period.

Conclusion: As seen in developed countries, rates of lung cancer in females are rising over the last three decades, but have not surpassed men rates yet. Adenocarcinoma is consistently the most frequent histological type in women. In men squamous cell rate has decreased.

Keywords: lung cancer, epidemiology, histology, gender

P1.01-054 LUNG CANCER IN BRAZIL: MEN AND WOMEN DIFFERENCES
Maria Teresa Ruiz Tsukazan1, Álvaro Vigo1, Vinicius Duval Da Silva1, Arthur Vieira1, Renata Rosenthal1, Flávio Cabral2, Gabriel Schwarcke1, João Schmitt1, Maicon Cimarost1, Jayme Rios1, José Antônio Figueiredo Pinto1
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P1.01-053 LUNG CANCER: HISTOLOGY, GENDER AND AGE CHANGES OVER PAST 30 YEARS IN BRAZIL
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1Hospital São Lucas Da Pucrs, Porto Alegre/Brazil, 2Universidade Federal Do Rio Grande Do Sul-Ufrgs, Porto Alegre/Brazil

Background: Lung is one of the leading causes of morbidity and mortality worldwide. It is most commonly attributed to smoking; a smaller proportion is attributed to occupational exposure. However, an earlier published study by Krishnamurthy et al 2012 from the authors institute reported the increasing trends of “Nonsmoking associated lung cancers” in the Indian subcontinent. A larger prospective study aimed at validating the initial findings was planned and this formed the basis of the present study. Methods: All consecutive histologically confirmed patients with lung cancer who presented to the outpatient department over a year (November 2014 to October 2015) were included in this current prospective study. A comprehensive questionnaire administered by a trained social worker captured all the demographic details including age, sex, occupation, smoking habits including exposure to second hand smoke, type of cooking fuel, histopathology and stage at presentation among others. (And later analyzed by SPSS Version 22.0) Results: 713 patients presented with clinicoradiological suspicious findings of lung cancer in the said period. A pathological confirmation of lung cancer could be ascertained in 605 patients and this cohort was further analyzed. The median age of presentation was 58 years; the male to female ratio was approximately 2.5:1. 52.12 % patients were nonsmokers. Adenocarcinoma (63 %) was the predominant histology. Nonsmokers, both among men (p=0.02) and women (p=0.001) presented more frequently with adenocarcinoma histology. Interestingly, 84.9 % (65/53) rural and 76.1 % (19/25) urban women who were nonsmoker reported exposure to indoor air pollution (second hand smoke/fuel used for cooking purposes) which was significantly associated with adenocarcinoma histology. (p=0.03) A majority of the patients (68.1 %) presented with clinical stage IV (7th edition TNM) Nearly 60% of patients presented in ECOG performance status 3-4, nonsmokers incidentally presented with clinical stage IV. (7th edition TNM) Nearly 60% of patients presented in ECOG performance status 3-4, nonsmokers incidentally presented in a better performance status than smokers (p=0.017). 53% of the patients unfortunately were deemed suitable only for best supportive care. Only 97 patients (18.6 %) were offered potentially curative treatment and radical surgery accounted for < 3 % of the overall management. Conclusion: This prospective study validated our initial observation of the increasing trends of lung cancers among nonsmokers. Further, this study also reflected the global trend of rise in adenocarcinoma histology. These findings in a larger perspective will help clinicians better understand the magnitude and the direction of the lung cancer epidemic and also aid policymakers in better channelizing the resources for effective public health interventions.

Keywords: smoking, lung cancer, epidemiology, Adenocarcinoma

P1.01-055 CLINICOEPIDEMIOLOGICAL TRENDS OF LUNG CANCER FROM A PREMIER REGIONAL CANCER CENTRE IN SOUTH INDIA
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Background: Lung Cancer is one of the leading causes of morbidity and mortality worldwide. It is most commonly attributed to smoking; a smaller proportion is attributed to occupational exposure. However, an earlier published study by Krishnamurthy et al 2012 from the authors institute reported the increasing trends of “Nonsmoking associated lung cancers” in the Indian subcontinent. A larger prospective study aimed at validating the initial findings was planned and this formed the basis of the present study. Methods: All consecutive histologically confirmed patients with lung cancer who presented to the outpatient department over a year (November 2014 to October 2015) were included in this current prospective study. A comprehensive questionnaire administered by a trained social worker captured all the demographic details including age, sex, occupation, smoking habits including exposure to second hand smoke, type of cooking fuel, histopathology and stage at presentation among others. (And later analyzed by SPSS Version 22.0) Results: 713 patients presented with clinicoradiological suspicious findings of lung cancer in the said period. A pathological confirmation of lung cancer could be ascertained in 605 patients and this cohort was further analyzed. The median age of presentation was 58 years; the male to female ratio was approximately 2.5:1. 52.12 % patients were nonsmokers. Adenocarcinoma (63 %) was the predominant histology. Nonsmokers, both among men (p=0.02) and women (p=0.001) presented more frequently with adenocarcinoma histology. Interestingly, 84.9 % (65/53) rural and 76.1 % (19/25) urban women who were nonsmoker reported exposure to indoor air pollution (second hand smoke/fuel used for cooking purposes) which was significantly associated with adenocarcinoma histology. (p=0.03) A majority of the patients (68.1 %) presented with clinical stage IV (7th edition TNM) Nearly 60% of patients presented in ECOG performance status 3-4, nonsmokers incidentally presented in a better performance status than smokers (p=0.017). 53% of the patients unfortunately were deemed suitable only for best supportive care. Only 97 patients (18.6 %) were offered potentially curative treatment and radical surgery accounted for < 3 % of the overall management. Conclusion: This prospective study validated our initial observation of the increasing trends of lung cancers among nonsmokers. Further, this study also reflected the global trend of rise in adenocarcinoma histology. These findings in a larger perspective will help clinicians better understand the magnitude and the direction of the lung cancer epidemic and also aid policymakers in better channelizing the resources for effective public health interventions.

Keywords: smoking, lung cancer, epidemiology, Adenocarcinoma

P1.01-056 LUNG CANCER EPIDEMIOLOGY IN CROATIA
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Poster SESSION 1 - P1.01: EPIDEMIOLOGY, TOBACCO CONTROL AND CESSATION/ PREVENTION DESCRIPTIVE EPIDEMIOLOGY - MONDAY, DECEMBER 5, 2016
Abstracts

University Hospital "split", Split/Croatia

Background: To analyze principal histological types of lung cancer, as well as sex and the age of patients, staging, tumor location, smoking history, Chronic obstructive pulmonary disease (COPD) history, and survival of lung cancer patients in Croatia. Methods: This was a retrospective study based on the analysis of medical charts of patients treated at the University Hospital "split", Split, Croatia in 2015 and 2016, and the 1-month period from January 2015 to February 2016, 332 patients with lung cancer, most of whom (75,30%) were male, were treated. Patients were between 36 and 85 years, with median age 65.5 years. There were 273 (84,78%) patients with NSCLC (Non-Small Cell Lung Cancer) and 49 (15,22%) patients with SCLC (Small Cell Lung Cancer). The most common histological type in patients with NSCLC was adenocarcinoma (58%), followed by squamous cell carcinoma (38%), NSCLC NOS (not otherwise specified) (2%), adenosquamous carcinoma (1%) and large cell carcinoma (1%). Among patients with NSCLC 13% are EGFR positive. Patients mostly had lung cancer in right lung (38,3%), most of them were smokers (88,4%), 20,70% patients had COPD and 21,05% patients had pleural adhesion. Concerning staging, 73,80% patients had stage IIB and IV at the time of diagnosis, and the remaining 26,20% were classified as stage I-IIIA. The principal sites of metastases where lungs (24,45%), bones (23,0%), and liver (12,9%). One-year survival was 23,21% and median overall survival was 8.82 months for patients presented with stage IIB and IV. Median age at death was 67.5 years. Conclusion: In accordance with the literature most of the lung cancer patients in Croatia are men, older age (but younger compared to developed countries), the most common histological type is adenocarcinoma. Most of the patients have cancer in the right lung, most of them are smokers and minority had COPD or pleural effusion. Most cases are presented in advanced stages at the moment of diagnosis. This affects on survival rate, which is lower compared to developed countries. To increase survival rate in Croatia lung cancer cessation should be encouraged, lung cancer screening, diagnosis and therapy should be improved, patients should be included in clinical trials and palliative care for terminal patients should be improved.

Keywords: lung cancer, epidemiology, Croatia

POSTER SESSION 1: P.01:01 EPIDEMOLOGY, TOBACCO CONTROL AND CESSATION/ PREVENTION
DESCRIPTIVE EPIDEMIOLOGY – MONDAY, DECEMBER 5, 2016

P1.01-057 METASTATIC LUNG CANCER AT A TERTIARY CANCER CENTRE IN SOUTH INDIA
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Background: Non-small cell lung cancer (NSCLC) has varying epidemiological patterns in different countries and also in different regions of each country. In a country with a high prevalence of lung cancer such as India, regional variations in demography exist. Methods: We did a retrospective analysis of histologically confirmed NSCLC patients who presented to our Department of Medical Oncology between August 2012 and 2014. The patients were interviewed regarding their history of smoking (never smokers, light smokers, and heavy smokers). Never smokers were defined as those who have never smoked >100 bids/cigarettes in their life until disease onset. Light smokers were defined as those who smoked ≤100 bides/cigarette per pack years. Heavy smokers were defined as those who smoke more than 100 bids/cigarette pack years until disease onset. All lung cancer biopsy specimens were histologically characterized by morphology and immunohistochemistry (IHC). A diagnosis of AC was made if IHC staining was positive for CK7, TTF1, and napsin A, similar to SCC was diagnosed if CK5/6 and p63 staining was positive. After confirmation of the histology subtype, patients were confirmed to have metastatic disease after assessment with contrast-enhanced computerized tomography thorax, abdomen scan, and radionuclide bone scan. Results: Our study did not include the small cell lung cancer patients. The data were analyzed on SPSS version 22 (IBM) software. Results: A total of 304 patients were analyzed. About 55.6% of the patients were in the age group of 41–60 years. About 79.6% of the patients were symptomatic for <6 months before presentation. About 63.5% of the patients were smokers presenting with a medical history of 15 years, whereas nonsmokers formed 36.5% of the patients with a medical age of 47 (P < 0.001). About 82.6% of the male patients and 4.6% of female patients were smokers. Equal number of all patients had adenocarcinoma (AC) and squamous carcinoma (SCC) histology. AC histology was more common in the nonsmoking group (62% of patients). SCC histology was seen in 54.8% of smokers. Metastatic disease to the contralateral lung and pleura was seen in 58.2% of patients. Conclusion: NSCLC presents at a young age. Smoking is a significant risk factor and it is common in the urban populations as in the rural areas. Both AC and SCC histologies presented in equal proportions.

Keywords: non small cell lung cancer, south India

POSTER SESSION 1: P.01:01 EPIDEMOLOGY, TOBACCO CONTROL AND CESSATION/ PREVENTION
DESCRIPTIVE EPIDEMIOLOGY – MONDAY, DECEMBER 5, 2016

P1.01-058 DEMOGRAPHIC PROFILE OF LUNG CANCER FROM EASTERN INDIA
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Background: The clinicopathological profile of primary lung cancer has changed considerably over the last few decades in India. Available literature suggests that the features of lung cancer in India like prevalence, incidence, age, pathogenesis and presentation vary markedly from the west. We performed a prospective evaluation of the unique demographic features of lung cancer with specific emphasis on smoking and histopathological trends. Methods: We analysed all pathologically proven lung cancer cases registered over a period of initial 30 months in the department of Pulmonary Medicine of the All India Institute of Medical Sciences, Bhubaneswar. The patients were evaluated for their epidemiological, clinical and pathological profiles. The data were recorded in MS Excel spreadsheets and subjected to appropriate statistical analysis. Data was collected directly from patients' paper and electronic medical records. All patients of histologically proven lung cancer were included. Results: A total of 179 patients were included in the database of which 6 patients were excluded for significant missing data. There were 114 male and 59 women average age 57.26 with a M:F ratio of 1.93:1. Over half (56%) of the patients were active or past smokers, while 48% patients had not been exposed to active or passive smoking. Bid (tobacco flake wrapped in tendu leaf) smoking was more common (37%) than cigarettes (19%) while 9% smoked both. Exclusive chewed tobacco use was seen in 12% while combined use of chewed and smoked tobacco was seen in 4% patients. The proportion of women never-smokers with lung cancer was significantly higher (89%) compared to men (28%). More than two-thirds patients (69.8%) presented with metastatic disease. Amongst patients with a definitive cytohistological diagnosis, the prevalence of adenocarcinomas was highest (56.3%) followed by squamous (30.8%), small cell (8%) and NSCLC NOS (4.9%). Conclusion: Adenocarcinoma is the commonest histological subtype in this region. Prevalence of lung cancer among non-smokers is also high in the eastern part of India. The demographic profile of patients with lung cancer in eastern India is unique with a much higher proportion of tobacco chewers and non-smoker especially in women. There is significant epidemiological trends towards a predominant adenocarcinoma histology. Most of the patients present at an advanced stage, probably due to limited diagnostic resources in this part of the country. Although there are direct association with smoking, there has been an increase in the non-smoking lung cancers worldwide.

Keywords: smoker, never-smoker, lung cancer, demography, India

POSTER SESSION 1: P.01:01 EPIDEMOLOGY, TOBACCO CONTROL AND CESSATION/ PREVENTION
DESCRIPTIVE EPIDEMIOLOGY – MONDAY, DECEMBER 5, 2016

P1.01-059 LUNG CANCER EPIDEMIOLOGY AMONG THE BAHRAINI POPULATION, 2000-2011
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Background: Lung cancer is the fourth most common cancer in the Gulf Cooperation Council countries among males and the third among females. It is the commonest cancer among Bahraini males accounting to 16.9% of all cancers and the third in Bahraini females contributing to 5.8% of all female cancers. The aim of this study was to describe the epidemiology of lung cancer among the Bahraini population during the period 1998-2011. Methods: All Bahraini registered lung cancer cases in the national cancer registry from 1 January 1998 to 31 December 2011 were included in the study. Incidence rates were calculated using the CANREG software, in which the annual crude incidence rates, age specific incidence rates and the age standardized incidence rate (ASR) were computed. Results: Six hundred sixty four lung cancer cases (72.4%, males and 27.6% females) were diagnosed during the study period. The annual average number of cases was 47.5 per year. The mean age at diagnosis during the study period was 70.1 years. The average annual ASR was 26.1/100,000 among males and 10.0/100,000 among females. There was a tendency for a decreased trend of the ASR during 1998-2011 in both sexes. Twenty six percent of lung cancer cases were squamous cell carcinoma and 17.9% adenocarcinoma. The grades of 70.3% were unknown and 13.4%
were poorly differentiated. The stage was unknown for 65.0% of the cases, while 18.5% had distant metastasis and 9.8% were localized. The majority (88.5%) of the lung cancer cases were dead by the end of the study period with a five-year survival rate of 3.0%. Conclusion: A welcomed decline in the incidence of lung cancer has been noted over the past 14 years. However, more efforts should be put to reduce the proportion of lung cancer cases with unknown stage and grade. The incidence of histological types, which are strongly dependent on tobacco smoking, notably small cell, squamous cell and large cell carcinomas, accounted for over one-third of lung cancer cases. Future research should be directed towards better understanding of the lung cancer risk factors and the effectiveness of tobacco control measures in the country.

Keywords: Trends, Cancer Registry, epidemiology, lung cancer

POSTER SESSION 1 - P1.02: BIOLOGY/PATHOLOGY
Driver Genes in NSCLC, Resistance, and Other – MONDAY, DECEMBER 5, 2016

P1.02-001 EXPRESSIONS OF RESISTANCE EGFR TKIs IN NON SMALL CELL LUNG CARCINOMA PHAM NGO THACH HOSPITAL - VIET NAM

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Background: In the patients with NSCLC were tested for diagnostic EGFR mutation, in addition to activating mutations, such as Exon 19 Deletion & Exon 21 L858R that is occupies a large amount. The mutation is said to be resistant to EGFR TKIs occupies smaller amount. However, this is also a challenge for the care and treatment for patients with NSCLC. Methods: Retrospective, cross-sectional descriptive statistics, clinical case series. Results: PRIMARY MUTATIONS WITH EGFR TKIs RESISTANCE §Activating EGFR Mutations: Exon 19 Deletion: 356/597 cases = 59.63% and Exon 21 L858R: 176/597 cases = 29.48%. §Primary Mutations with EGFR TKIs Resistance - Single mutations: 46/597 cases = 7.71% (Male: 27 cases + Female: 19 cases), including: Exon 20 Insertion: 25 cases, Exon 18 G719X: 14 cases, Exon 20 S768I: 5 cases, Exon 20 T790M: 2 cases. §Primary Mutations with EGFR TKIs Resistance - Double mutations: 19/597 cases = 3.18% (Male: 11 cases + Female: 8 cases), including: Exon 21 L858R + Exon 20 T790M: 6 cases, Exon 19 Deletion + Exon 20 T790M: 5 cases, Exon 18 G719X + Exon 20 Insertion: 2 cases, Exon 21 L858R + Exon 20 G776R: 3 cases, Exon 18 G719X + Exon 20 S768I: 3 cases. ACQUIRED MUTATIONS WITH EGFR TKIs RESISTANCE §Total cases with the gene mutation diagnosis repeating again (Sampling with Histology or Cytology): 113/597 cases (18.93%). Detection rate for new resistance EGFR TKIs mutations: Number of Cases: 56 cases; T790M + G719X: 2 cases; T790M + G719A: 3 cases; T790M + A763V: 4 cases; T790M + L777G: 1 case; T790M + Y801C: 3 cases; T790M + Q774X: 2 cases; T790M + S768I: 3 cases. DRUG RESISTANT MUTATIONS WITH EGFR TKIs RESISTANCE §There are 3 both IHC/RT-PCR positive cases by IHC staining, and the mutations system kits(AmoyDx), ALK and RET fusion was tested by RT-PCR confirmation test. Some other lung cancer driver genes were also detected in non-small cell lung cancer (NSCLC). The clinical trial showed that NSCLC patients harboring ROS1 fusion could benefit from crizotinib treatment. Several studies reported that immunohistochemistry (IHC) could be employed as a screening method for detecting ROS1 fusion in tumor tissue using Anti-ROS1(D4D6) antibody. Malignant pleural effusion (MPE) is the common sample type in advanced NSCLC, the reliability of ROS1(D4D6) for detecting ROS1 fusion in MPE-cell blocks (CBS) should be explored. Methods: Anti-ROS1(D4D6) monoclonal antibody (Cell Signaling Technology, Danvers, USA) IHC testing was performed on 227 formalin fixed paraffin embedded (FFPE) MPE CBS from lung adenocarcinoma patients. RT-PCR using ROS1 fusion gene detection kit (AmoyDx) was performed to detect ROS1 gene fusion as a confirming test. Some other cancer driver genes were also detected in both IHC/RT-PCR ROS1 positive samples, among which EGFR, KRAS, BRAF, PIK3CA and HER2 20 exon mutation was tested by amplification refractory mutation system kit(AmoyDx), ALK and RET fusion was tested by RT-PCR kits(AmoyDx). Results: 4 of 227 MPE samples(1.76%) of lung adenocarcinoma were interpreted as ROS1 fusion-positive cases by IHC staining, and the cytoplasmic and membranous granular positive signals were displayed. Comparison with RT-PCR testing results, 3 of 4 IHC positive cases were verified by RT-PCR, the sensitivity was 100% and specificity of was 99.6%. The clinicopathologic features and other genes status of 3 both IHC/RT-PCR positive patients were showed in Table 1. One ROS1 IHC/RT-PCR positive lung adenocarcinoma patient received crizotinib therapy and obtained partial response. Conclusion: ROS1(D4D6) would be a reliable antibody for screening ROS1 fusion-positive lung adenocarcinoma on FFPE MPE CBS by IHC assay and shows high specificity in the FFPE MPE CBS samples.
Keywords: non-small cell lung cancer, ros1, Immunohistochemistry, RT-PCR

Background: Epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors have improved the outcome of patients with EGFR-mutated lung adenocarcinoma (ADC). However, EGFR mutation occurred in about only 10-15% of ADC, but other alterations are emerging as potential targetable drugs. We analyzed the frequency of potentially targetable driver alterations in a series of advanced EGFR-wild type (wt) NSCLC patients. Methods: 724 advanced EGFR-wt NSCLC patients enrolled from the Wide Catchment Area of Romagna (AVR) between January 2013 to December 2014 were included in the study. KRAS, BRAF, ERBB2, PIK3CA, NRAS, ALK, MAP2K1, RET and DDR2 mutations were analyzed by Myriapod® Lung Status kit (Dia tex Pharmaceuticals) on MassARRAY® (SEQUENOM Inc, California). EGFR was evaluated by direct sequencing and EML4-ALK and ROS1 rearrangements were assessed by immunohistochemistry or fluorescence in situ hybridization. Results: 331 (45.7%) patients showed at least one alteration. Of these, 72.2%, 6.3%, 3.6%, 1.8%, 2% and 1.2% patients had mutations in KRAS, BRAF, PIK3CA, NRAS, ERBB2 and MAP2K1 genes, respectively. Only one patient showed a mutation in EGFR. EML4-ALK and ROS1 rearrangements were observed in 4.3% and 1.4% of all patients, respectively. The distribution of mutations in relation to gender and smoking habits is reported in the Table. Overlapping mutations were observed in 7 KRAS-mutated patients: 2 (28.6%) patients were also mutated in PIK3CA, 4 (57.1%) showed also an EML4-ALK translocation and one (14.3%) had a ROS1 rearrangement. One (0.3%) patient showed both BRAF and PIK3CA alterations. Correlation analyses between the different mutations and patient outcome are ongoing.

Keywords: driver alterations, EGFR wt, MassARRAY

<table>
<thead>
<tr>
<th>GENE</th>
<th>Mutated Patients (%)</th>
<th>Smoker (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>KRAS</td>
<td>239 (33)</td>
<td>93 (39)</td>
</tr>
<tr>
<td>BRAF</td>
<td>21 (3)</td>
<td>11 (52.4)</td>
</tr>
<tr>
<td>NRAS</td>
<td>6 (0.8)</td>
<td>4 (66.7)</td>
</tr>
<tr>
<td>PIK3CA</td>
<td>12 (1.6)</td>
<td>4 (33.3)</td>
</tr>
<tr>
<td>MAP2K1</td>
<td>4 (0.5)</td>
<td>4 (100)</td>
</tr>
<tr>
<td>ERBB2</td>
<td>7 (0.9)</td>
<td>5 (71.4)</td>
</tr>
<tr>
<td>EML4-ALK</td>
<td>31 (4.3)</td>
<td>20 (64.5)</td>
</tr>
<tr>
<td>ROS1</td>
<td>10 (1.4)</td>
<td>7 (70)</td>
</tr>
</tbody>
</table>

*: some data are missing

Conclusion: Driver mutations were detected in about 50% of EGFR wt lung ADC patients. Such alterations could represent potential targets for therapy and could be evaluated in routine multiplexed testing to obtain a wider tumor molecular characterization.

Keywords: driver alterations, EGFR wt, MassARRAY

POSTER SESSION 1: P1.02: BIOLOGY/PATHOLOGY DRIVER GENES IN NSCLC, RESISTANCE, AND OTHER – MONDAY, DECEMBER 5, 2016

P1.02-004 A RETROSPECTIVE ANALYSIS OF FREQUENCY OF ALK GENE REARRANGEMENT IN SAUDI LUNG PATIENTS

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Background: Lung carcinoma represents 2.9% of cancers seen at King Faisal Specialist Hospital and Research Centre (KFSH&RC) as per KFSH&RC Tumor Registry (2010). EML4-ALK re-arrangement play an important oncogenic driver role in lung adenocarcinoma tumorgenesis in 3-5% of cases. ALK gene rearrangement (inversion in chromosome 2) testing can identify patients with adenocarcinoma who are sensitive to ALK tyrosine kinase inhibitors. No data is available on the prevalence of ALK rearrangement changes in Saudi lung cancer patients. The aim of this study is to evaluate the prevalence of ALK gene rearrangement in lung adenocarcinoma of Saudi patients. Methods: A total of 172 cases of lung adenocarcinoma diagnosed at KFSH&RC between January 2013 to May 2016 were identified. Formalin-fixed paraffin embedded tissue samples of these patients were analyzed for ALK gene rearrangement using fluorescence in situ hybridization (FISH), utilizing break-apart probes from Vysis (Abbott Molecular, IL, USA). Results: Eleven (11) cases exhibited ALK gene rearrangement (6.4%). Nine out of eleven cases were stage IV and two cases were stage III. Median patients age was age 47 years (21-71 years) with male predominance (males 77%, female 25%). All cases were moderately to poorly differentiated adenocarcinoma. None of our cases showed signet ring cells or predominant adenocarcinoma (males 77%, female 25%). All cases were moderately to poorly differentiated adenocarcinoma. None of our cases showed signet ring cells or abundant intracellular mucin. Conclusion: Our findings showed the incidence of ALK gene rearrangement in lung adenocarcinoma in Saudi patients is 6.4%. This is slightly higher in comparison to the published data which may be attributed to KFSH&RC being a tertiary referral Center.

Keywords: lung adenocarcinoma, ALK rearrangement

POSTER SESSION 1: P1.02: BIOLOGY/PATHOLOGY DRIVER GENES IN NSCLC, RESISTANCE, AND OTHER – MONDAY, DECEMBER 5, 2016

P1.02-005 FREQUENCY OF ACTIONABLE ALTERATIONS IN EGFR WT REARRANGEMENT IN SAUDI LUNG PATIENTS

MONDAY, DECEMBER 5, 2016

P1.02-006 INTERLABORATORY VARIATION IN MOLECULAR TESTING (EGFR, KRAS AND ALK) IN STAGE IV NON-SQUAMOUS NON-SMALL CELL LUNG CANCER IN THE NETHERLANDS IN 2013

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Background: Adequate testing for molecular changes in non-small cell lung cancer (NSCLC) is necessary to ensure the best possible treatment. However, it is unknown how well molecular testing is performed in daily practice. Therefore we aimed to assess the performance of testing for EGFR, KRAS mutation and ALK translocation in metastatic NSCLC on a nationwide basis. Methods: Using the Netherlands Cancer Registry, all stage IV non-squamous NSCLC from 2013 were identified and matched to the Dutch Pathology Registry (PALGA). Data on molecular testing for EGFR, KRAS and ALK were extracted from excerpts of pathology reports. Proportions of tested and positive cases were determined and interlaboratory variation was assessed. Finally, degree of concordance between ALK immunohistochemistry (IHC) and fluorescent in situ hybridization (FISH) results was evaluated. Results: In total, 3393 stage IV non-squamous NSCLCs were identified, and 3183 (93.8%) were matched to PALGA. Fifty-two tumors were excluded as pathology

<table>
<thead>
<tr>
<th>GENE</th>
<th>Mutated Patients (%)</th>
<th>Smoking Habits*</th>
</tr>
</thead>
<tbody>
<tr>
<td>KRAS</td>
<td>239 (33)</td>
<td>93 (39)</td>
</tr>
<tr>
<td>BRAF</td>
<td>21 (3)</td>
<td>11 (52.4)</td>
</tr>
<tr>
<td>NRAS</td>
<td>6 (0.8)</td>
<td>4 (66.7)</td>
</tr>
<tr>
<td>PIK3CA</td>
<td>12 (1.6)</td>
<td>4 (33.3)</td>
</tr>
<tr>
<td>MAP2K1</td>
<td>4 (0.5)</td>
<td>4 (100)</td>
</tr>
<tr>
<td>ERBB2</td>
<td>7 (0.9)</td>
<td>5 (71.4)</td>
</tr>
<tr>
<td>EML4-ALK</td>
<td>31 (4.3)</td>
<td>20 (64.5)</td>
</tr>
<tr>
<td>ROS1</td>
<td>10 (1.4)</td>
<td>7 (70)</td>
</tr>
</tbody>
</table>

*: some data are missing

Conclusion: Driver mutations were detected in about 50% of EGFR wt lung ADC patients. Such alterations could represent potential targets for therapy and could be evaluated in routine multiplexed testing to obtain a wider tumor molecular characterization.

Keywords: driver alterations, EGFR wt, MassARRAY
reports described a lung tumor other than non-squamous NSCLC or a tumor with another origin, leaving 3131 tumors. All 48 laboratories had access to molecular testing, either in house or via outsourcing. The table shows the nationwide proportions of cases tested and positive for EGFR, ALK, and ALK as well as the interlaboratory variation. EGFR and KRAS mutations occurred together in 8 patients; ALK translocation occurred together with EGFR mutation in 3 patients and with KRAS mutation in 2 patients. In 272 cases, ALK had been tested using both IHC and FISH, and the methods were conclusive in 233 cases. IHC and FISH were concordant in 233 cases (94.5%; Kappa 0.728, p=0.069), 5 discordant cases were IHC+/FISH- and 9 were IHC-/FISH+.

Conclusion: These results suggest that in 2013 molecular testing was suboptimal in the Netherlands, especially for ALK. To determine whether molecular testing has improved, 2015 data will be analyzed in the near future as well.

Keywords: non-small cell lung cancer, molecular testing, interlaboratory variation, quality assessment
the intra-tumor heterogeneity of ALK RNA-ISH by counting 100 tumor cells in 10 different loci (total, 1000 tumor cells) in each tumor. Secondly, we analyzed the diagnostic accuracy of ALK RNA-ISH in tissue microarrays (TMA) containing 294 lung adenocarcinoma cases (ranging from 100 tumor cells in each core) with no information about ALK gene rearrangements and compared these results with those of conventional IHC and FISH tests. Results: ALK mRNA expression was observed in all 11 resected lung adenocarcinomas by the ALK RNA-ISH assay and the median of positive tumor cells was 67.7%, whereas ALK mRNA expression was not observed in normal lung cells in the background. Next, 5 ALK positive cases were found by IHC and/or FISH in the 294 cases of lung adenocarcinoma. The median of positive cells by ALK RNA-ISH in these 5 cases was 75.6% (range: 40-94%), whereas the median of positive cells by ALK ALK RNA-ISH in the remaining 289 cases was 0.3% (range: 0-15%). When the cutoff value was set as 15% based on the first test, the ALK RNA-ISH–positive and ALK RNA-ISH–negative cases were readily distinguishable with 100% sensitivity and specificity compared with the results of IHC and/or FISH. Conclusion: Our findings suggest that the ALK RNA-ISH assay is useful for detecting ALK positive lung adenocarcinomas with high sensitivity and specificity compared with the conventional IHC and FISH test. Thus, this study provides important and timely insight into the clinical testing of ALK in lung cancer because the RNA-ISH assay detects the target mRNA easily and rapidly.

Keywords: ALK, lung adenocarcinoma, RNA in situ hybridization

Poster Session 1: P1.02 Biology/Pathology Driver Genes in NSCLC, Resistance, and Other – Monday, December 5, 2016

P1.02-010 FREQUENCY OF UNCOMMON EGFR MUTATIONS IN NSCLC IN AN ARGENTINEAN UNIVERSITY INSTITUTION

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Background: EGFR mutations are present in approximately 15% of NSCLC Caucasian patients, with a similar frequency described in Argentina. Exon 19 deletions and exon 21 L858R are consider common mutations (90%) that predict better progression free survival with EGFR-TKIs than with chemotherapy treatment. Most relevant uncommon mutations had a frequency ranged from 1.9% to 7.9% between different populations and their outcome, in general, is less favorable. Methods: We analyzed, retrospectively, our database of EGFR mutational status in the last two years with the objective to describe the frequency and characteristics of the patients with uncommon EGFR mutations in our population of NSCLC patients. The mutational analysis was performed on formalin fixed paraffin-embedded tissue blocks. EGFR exons 18 through 21 were amplified by PCR-based technology. Results: A total of 113 patients underwent EGFR testing since January 2014 until June 2016. Among them, 28 cases (25.7%) harbored EGFR mutations. The exon 19 deletions (n=9; 8%) and L858R point mutation (n=6; 5.3%) accounted for the 51.7% of EGFR mutated cases (13.3% of the population explored) while 48.3% were uncommon mutations (12.4%). In the last group, mutations sites were: G719X in exon 18 (n=9; 8%), L861Q in exon 21 (n=1; 1.8%), INS20 in exon 20 (n=1; 1.8%) and S768I in exon 20 (n=1; 0.9%). All the 14 patients carrying these EGFR uncommon mutations had adenocarcinoma histology. In addition, they were more frequently observed in men than in women (79% versus 21%) and were more frequently observed in men than in women (79% versus 21%) and in smokers than in non-smokers (65% versus 45%). The mean age was 62.5 years. Most of the patients (n=11; 75.6%) had advanced disease (stage IIIb-IIIV) at diagnosis. No one had Asian ethnicity. Seven patients (50%) received EGFR-TKIs at first or second line treatment (4 erlotinib, 2 afatinib and 1 gefitinib). None of them showed sustained clinical benefit. At present, 7 out of 12 patients had died. Conclusion: Although the clinical characteristics of our cohort are similar to the data published, we noted a higher and unusual frequency of EGFR uncommon mutations especially exon 18 G719X. All cases treated with EGFR-TKIs showed poor sensitivity to therapy. Time to treatment and accessibility to appropriate therapy in this subgroup are important issues to explore in future reports from public institutions of our region.

Keywords: EGFR mutation, TKI, NSCLC

Poster Session 1: P1.02 Biology/Pathology Driver Genes in NSCLC, Resistance, and Other – Monday, December 5, 2016

P1.02-011 COMPARISON OF EGFR AND KRAS MUTATIONS IN NSCLC AND RESISTANCE TO EGFR-TKIS TO EXPLORER IN FUTURE REPORTS FROM PUBLIC INSTITUTIONS OF OUR REGION

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Background: In non-small cell lung cancer (NSCLC), circulating tumor DNA (ctDNA) has gained acceptance as a potential alternative to tissue biopsies to identify targetable mutations. Individual ctDNA platforms have varying abilities to detect specific mutations. A prospective, multicenter study was conducted to determine concordance, sensitivity, and specificity of ctDNA genotyping, with archival tissue DNA (atDNA) as the reference standard. Methods: Patients with incurable advanced NSCLC at the BC Cancer Agency were enrolled over 14 months. Next-Generation Sequencing (NGS) and high-throughput multiplex amplification of a 27-gene panel (Raindance) was used for atDNA analysis. Four ml of plasma was collected in Streck (Cell Free DNA BCT) tubes for ctDNA genotyping using the Boreal Genomic OnTarget. Analysis of concordance, sensitivity, and specificity was conducted with atDNA used as the standard. Results: Seventy-six patients were enrolled, median age 66, 33 (44.4%) male, 69 (91%) metastatic disease, 47 (62%) with primary disease in situ. Twenty-six EGFR mutations in 22 atDNA samples, and 12 mutations in 11 ctDNA samples were detected, with a concordance of 78%, sensitivity of 39%, and specificity 98%. One EGFR T790M mutation was positive by ctDNA alone. Twenty-one KRAS mutations in 21 atDNA samples were detected. Within this subgroup, 10 atDNA samples had KRAS mutations with a concordance of 76%, sensitivity of 50%, and specificity of 80%. Fourteen KRAS mutations were detected by ctDNA only. The interval between archival tissue and ctDNA collection, and time between treatment and ctDNA collection, did not significantly impact the rate of concordance (p = 0.05). Conclusion: Although the sensitivity is limited, the Boreal Genomic OnTarget ctDNA analysis is specific in identifying clinically relevant EGFR mutations and has acceptable concordance rates between ctDNA and atDNA testing. Targetable EGFR and KRAS mutations were detected in ctDNA but not atDNA, which may reflect site of biopsy, tumor heterogeneity, or technical limitations of assays used. Given the high specificity and non-invasive nature of this test, positive results in EGFR mutations can be used to direct therapeutic decisions, especially accounting for clonal evolution overtime in detection of resistance mutations.

Keywords: NSCLC, ctDNA, EGFR, KRAS

Poster Session 1: P1.02 Biology/Pathology Driver Genes in NSCLC, Resistance, and Other – Monday, December 5, 2016

P1.02-012 FREQUENCIES OF ACTIONABLE MUTATIONS AND SURVIVAL IN VARIANTS OF INVASIVE ADENOCARCINOMA OF THE LUNG

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Background: 2015 new WHO classification lists four rare variants of invasive adenocarcinoma of the lung (VIA): invasive mucinous adenocarcinoma, colloid adenocarcinoma, fetal adenocarcinoma and enteric adenocarcinoma. Very little information is known regarding the molecular alterations and prognostic values for rarity of VIA. The aim of present study was to investigate the common actionable mutations and survival in VIA. Methods: Patients who with pathologic confirmed as VIA with completely resected stage I-IIIA were enrolled from 2010 to 2013. For comparison, we evaluated the gene status and survival from 380 non-VIA lung adenocarcinoma patients in 2012. RT-PCR was utilized for detecting the mutations of EGFR, KRAS, NRAS, PIK3CA, BRAF, HER2 and the fusion of ALK, ROS1 and RET. Survival curves were plotted with Kaplan-Meier method. Results: Thirty one patients were recruited from 1120 lung adenocarcinoma, including invasive mucinous adenocarcinoma (n=15), enteric adenocarcinoma (n=9), colloid adenocarcinoma (n=4) and fetal adenocarcinoma (n=3). The overall frequency of gene abnormality in VIA was 48.4% (15/31). The genes abnormality was as follows: KRAS mutation (n=5), ALK rearrangement (n=4), PIK3CA (n=2), EGFR mutation (n=2), HER2 mutation (n=1) and ROS1 rearrangement (n=1). No mutations of NRAS, BRAF or RET were observed. The frequency of gene abnormality was lower in VIA than non-VIA patients (48.4% vs. 74.7%, P=0.0015). No recurrence free survival difference existed in the VIA and non-VIA patients (30.8 vs.47.0 months, P=0.524). A trend of worse overall survival in VIA than those with non-VIA patients was found(48.0 vs.57.0 months, P=0.052). Conclusion: VIA is rare in lung adenocarcinoma with lower frequency of common gene abnormality. Invasive mucinous adenocarcinoma was the most frequent subtype and KRAS was a predominant actionable mutation in VIA patients. A trend of worse survival existed in VIA than non-VIA patients.

Keywords: VIA, Lung carcinoma, Survival, Mutation
Keywords: non-small cell lung cancer, survival, variants of invasive adenocarcinoma, gene abnormality

P.01.02-013 CLINICOPATHOLOGICAL CHARACTERISTICS AND SURVIVAL OF ALK, ROS1 AND RET ARRANGEMENTS IN NON-ADENOCARCINOMA NON- SMALL CELL LUNG CANCER PATIENTS

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Background: ALK, ROS1 and RET rearrangements represent three most frequent fusion genes in non-small cell lung cancer (NSCLC). Rearrangements of the three genes are predominantly found in lung adenocarcinoma, while rare in non-adenocarcinoma. The aim of this study was to investigate the frequency, clinicopathological characteristics and survival of ALK, ROS1 and RET arrangements in non-adenocarcinoma NSCLC patients. Methods: We screened ALK, ROS1 and RET rearrangements in patients with completely resected non-adenocarcinoma NSCLC using reverse transcriptase polymerase chain reaction (RT-PCR). All positive samples were confirmed with fluorescence in situ hybridization (FISH). Survival analysis was performed with Kaplan-Meier method and log-rank for comparison. Results: Totally, 385 patients, who underwent complete resection, including 245 with squamous cell carcinoma, 85 with adenocarcinoma and 55 with large cell carcinoma were enrolled. Twelve patients were identified as harboring fusion genes, including seven with ALK, three with ROS1 and two with RET rearrangements. The frequencies of fusions in adenocarcinoma, squamous cell carcinoma, and large cell carcinoma were 8.2%, 1.6% and 1.8%, respectively. The median age of 12 patients was 49.5 years and three patients had smoking history. No survival difference existed between fusion gene positive and negative patients (36.7 vs 50.2 months, P=0.21). Conclusion: The frequencies of ALK, ROS1 and RET rearrangements are low in non-adenocarcinoma NSCLC patients, and the clinical characteristics are similar with those in lung adenocarcinoma. Fusions of the three genes are not prognostic marker for non-adenocarcinoma NSCLC patients.

Keywords: fusion gene, frequency, survival, non-small cell lung cancer

P.01.02-014 HER2 MUTATIONS IN CHINESE PATIENTS WITH NON- SMALL CELL LUNG CANCER

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Background: ERBB2 (HER2) is a driver gene identified in non-small cell lung cancer (NSCLC). The prevalence, clinicopathological, genetic variability and treatment of HER2-positive NSCLC in Chinese population is unclear. Methods: Eight hundred and fifty-nine patients with pathologically confirmed NSCLC were screened for HER2 mutations using Sanger sequencing. Next-generation sequencing (NGS) was performed in positive cases. HER2 amplification was detected with FISH. Overall survival (OS) was evaluated using Kaplan-Meier methods and compared with log-rank tests. Results: Twenty-one cases carrying HER2 mutations were identified with a prevalence of 2.4%. HER2 mutations were more frequently encountered in females, non-smokers and adenocarcinoma. NGS was performed in 19 out of 21 patients, The results showed 16 cases with additional genetic aberrations, most commonly associated with TP53 (n=6), followed by EGFR (n=3), NFI (n=3), KRAS (n=2) and other mutations. One patient harbored HER2 amplification (figure 1). Four patients with stage IV received afatinib treatment, and three showed stable disease with a median progression-free survival of 4 months and one patient was diagnosed with progressive disease. No survival difference existed between HER2 positive and negative patients (49.3 months vs 45.0 months, P = 0.15). Conclusion: HER2 mutations represent a distinct subset of NSCLC. NGS showed that HER2 mutations commonly co-existed with other driver genes. Afatinib treatment displayed moderate efficacy in patients with HER2 mutations.

Keywords: PREVALENCE, treatment, HER2 mutation, genetic variability

P.01.02-015 A MULTICENTER STUDY OF EGFR AND EML4-ALK DETECTION IN NON-SQUAMOUS, NON-SMALL-CELL LUNG CANCER PATIENTS WITH MALIGNANT PLEURAL EFFUSION

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Background: Currently, multicenter studies involving a large number of patients have not been not undertaken to detect the frequencies of EGFR mutations and ALK rearrangement in malignant pleural effusion (MPE) samples of patients with non-squamous, non-small-cell lung cancer (NSCLC). We undertook a multicenter, observational study of Asian patients with untreated stage IV NSCLC. Methods: Eligible patients had untreated of EGFR and ALK inhibitor stage IV non-squamous NSCLC patients with MPE. The EGFR and ALK status of MPE and partially paired tumor tissue was determined with reverse transcription polymerase chain reaction (RT-PCR). Results: Among 210 patients with pleural effusion samples confirmed as malignant, 16 had EML4-ALK fusion gene rearrangements and 89 had EGFR mutations. No ALK/EGFR coalterated gene was found. Tumor tissue of 56 patients were collected. EGFR and ALK concordance rates between MPE samples and matched tumor tissue samples from 56 patients were 87.5% (49/56) and 96.1% (49/51), respectively. There was a tendency for a longer progression free survival in patients with EGFR accordance in comparison with those with EGFR discordance between tumor tissue and MPE samples (9.8 vs 6.2 months, respectively; p = 0.078). A same trend was found in patients with ALK accordance and discordance (10.0 vs 3.2 months, respectively; p = 0.004). Conclusion: These results demonstrate that MPE can be substituted for tumor tissues for EGFR and ALK gene detection. Patients with gene mutations or arrangement discordance between tumor tissue and MPE samples showed an inferior efficacy of targeted therapy than those with accordance.

Keywords: Epidermal growth factor receptor, Anaplastic lymphoma kinase, malignant pleural effusion, Non-small-cell lung cancer

P.01.02-016 HER4 EXPRESSION WAS RELATED TO THE SENSITIVITY OF EGFR-TKI IN NON-SMALL CELL LUNG CANCER

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Background: EGFR-TKIs show significant therapeutic effects against non-small cell lung cancer (NSCLC) with EGFR-activating mutations, however 20-30% of them have no response to EGFR-TKIs. HER-family receptors play a critical role in tumor progression, differentiation and survival in lung cancer. Recent studies suggest that the overexpression of HER-family receptors have a potential risk of EGFR-TKIs resistance. The aims of this study were to investigate the association between EGFR-mutation and the expression of HER-family receptor in regard to clinical outcomes. Methods: We invested EGFR mutation by direct PCR analysis and HER2-4 expression by immunohistochemistry (IHC) of 231 consecutive non-small cell lung cancers, who had undertaken an operation from January 2007 to July 2012. The intensity of HER2-4 was graded (score: 0-3) from negative (score: 0-1) to positive (score: 2-3). The observed protein expression levels were analyzed for correlation to EGFR mutation status, clinicopathological parameters and the responses of EGFR-TKI treatment. Results: EGFR mutation was observed in 60% of lung cancer, 61% of p.Leu585Arg and 31% of exon 19 deletion. Positive expression rates of HER2, HER3 and HER4 were 22.9%, 1.2%, 38.5%, respectively. HER4 positive rare of EGFR positive group was significantly lower that of HER2 positive group (43% vs 26%, P=0.03). The response rate of EGFR-TKIs in HER2 positive group was low, but high in HER4 positive group. Conclusion: Our data showed that HER4 expression was independent form EGFR mutation and HER2 expression, but related to the sensitivity against EGFR-TKIs. HER4 positive patients may be candidate for pan-HER inhibitor augments.

Keywords: HER family receptor, EGFR mutation, non-small cell lung cancer
POSTER SESSION 1: P1.02 BIOLOGY/PATHOLOGY
DRIVER GENES IN NSCLC, RESISTANCE, AND OTHER – MONDAY, DECEMBER 5, 2016

P1.02-017 RELATIVE ABUNDANCE OF EGFR MUTATIONS PREDICT TUMOR METASTASIS AND EGFR-TKIS PROGNOSIS IN PATIENTS WITH NON-SMALL CELL LUNG CANCER
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Background: The most lethality in NSCLC is due to uncontrolled tumor metastasis. Epidermal growth factor receptor (EGFR) has been confirmed to be an effective biomarker in EGFR-TKIs treatment for advanced NSCLC. Previous studies have demonstrated EGFR mutation abundance could predict benefit from EGFR-TKIs treatment. However, there is no investigation on the correlation between EGFR mutation abundance and tumor metastasis. Here we aimed to explore potential effect of EGFR mutation abundance on tumor metastasis and EGFR-TKIs prognosis.

Methods: 3931 patients from Henan Cancer Hospital diagnosed with NSCLC were enrolled. The EGFR mutation abundance in tumor specimens was quantified by amplification refractory mutation system (ARMS). 16% was defined as high abundance, and below 16% was defined as low abundance. Results: The ratio of high mutation abundance in age <60 years group was significantly higher that than in age ≥60 years group (55.4% vs. 42.5%, P<0.000), similar distribution was also detected in 19 exon deletion and L858R subgroup (P=0.003 and 0.030, respectively). Whereas the distribution of EGFR mutation abundance was no difference between surgery and biopsy specimens (P=1.000). Additionally, the ratio of high abundance in 19 exon deletion was obviously higher than that in L858R and rare mutations (65.5% vs. 31.6% vs. 51.7%, P<0.000). Meanwhile, the ratio of high abundance in patients with hepar metastasis was significantly higher than that in patients without hepar metastasis (57.2% vs. 47.8%, P=0.036), but that in brain or bone metastasis was demonstrated no significant difference (P=0.897 and P=0.293, respectively).

Results: The subgroup analysis among above metastasis patients indicated the ratio of high abundance in 19 exon deletion was significantly higher than that in L858R. Furthermore, the difference in median PFS between 19 exon deletion and L858R subgroup was significant (17.5 months vs. 9.2 months, P=0.003). Conclusion: EGFR mutation abundance was not associated with the methods of collecting specimens, the kylhar high EGFR mutation abundance. Hepar metastasis status was associated with EGFR mutation abundance. Median PFS in 19 exon deletion patients was notably longer than that in L858R group for EGFR-TKIs treatment, which may refer to high abundance in 19 exon deletion.

Keywords: metastasis, Abundance, Prognosis, EGFR mutation.

POSTER SESSION 1: P1.02 BIOLOGY/PATHOLOGY
DRIVER GENES IN NSCLC, RESISTANCE, AND OTHER – MONDAY, DECEMBER 5, 2016

P1.02-018 OSTEOSARCOMATOUS DIFFERENTIATION IN THE REBIOPSY SPECIMENS OF PATIENTS HARBORING PULMONARY ADENOCARCINOMA WITH EGFR-TKI RESISTANCE
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Background: Histological transformation including small cell carcinoma and epithelial to mesenchymal transition (EMT) is one of the discovered mechanisms of the acquired resistance to EGFR-TKI. We report two cases of Epidermal Growth Factor Receptor-Tyrosine Kinase Inhibitor (EGFR-TKI) resistant pulmonary adenocarcinoma associated with EMT features that showed osteosarcomatous differentiation in rebiopsy specimens. Methods: We identified two patients with primary lung adenocarcinoma that showed osteosarcomatous transformation on second biopsy (n = 60) between 2010 and 2016. Histomorphologic features and EGFR mutation results were compared between initial and second biopsy samples. Results: Case 1 A 55-year-old female, non-smoker presenting chronic cough was confirmed to have pulmonary adenocarcinoma harboring EGFR exon 19 deletion mutation with disseminated intrapulmonary metastasis. After 1 year of gefinitib treatment, radiologic evaluation showed left iliac metastases with extrasternal ossification. Case 2 A 58-year-old man who had undergone right upper lobectomy of the lung was diagnosed as adenocarcinoma with pT1N0M0 harboring an EGFR exon 19 deletion mutation. Three years after surgery, metastatic lesions developed in the right lower lobe and pleura. After 15 months of conventional chemotherapy, 2nd biopsy for the pulmonary lesion confirmed 1790M mutation and additional metastatic lesions found in T2 and T5 vertebral bodies were removed by surgical curettage. Rebiopsy of the metastatic bone lesions of these two patients showed metastic adenocarcinoma merging with poorly differentiated sarcomatous components. Remarkably, the spindle shaped sarcomatous tumor cells produced ill-defined eosinophilic lace-like osseoid. These osseoid components were closely associated with the tumor cells and deposited as disorganized features. The sarcomatous neoplastic cells intermingled with osseoid demonstrate unequivocal features of malignancy, which is different from reactive osseofibrosis or callus formation. EGFR mutation status were same from that of primary lung specimen and IHC showed vimentin expression and decreased E-cadherin (EMT feature). Conclusion: To the best of our knowledge, this is the first report to describe pulmonary adenocarcinoma with osteosarcomatous differentiation in rebiopsy specimens of EGFR-TKI resistant patients. As the evaluation of metastatic sites for rebiopsy were bone lesions in both patients, the role of the tumor microenvironment may support the transformation from adenocarcinoma to osteosarcomatous phenotype. A few previous studies suggested that a bone environment is essential for osteosarcoma development from transformed mesenchymal stem cells. Our findings suggest that the differences of the intrinsic nature between epithelial and osteosarcomatous mesenchymal cancers may be the cause of the acquired resistance of EGFR-TKI.

Keywords: pulmonary adenocarcinoma, osteosarcomatous differentiation, EGFR-TKI resistance, rebiopsy.

POSTER SESSION 1: P1.02 BIOLOGY/PATHOLOGY
DRIVER GENES IN NSCLC, RESISTANCE, AND OTHER – MONDAY, DECEMBER 5, 2016

P1.02-019 COMPLEX MUTATION OF EPIDERMAL GROWTH FACTOR RECEPTOR (EGFR) IN PATIENTS WITH NON-SMALL LUNG CANCER
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Background: Analysis of the epidermal growth factor receptor (EGFR) gene is currently one of the most important tests in establishment of a treatment strategy for primary lung cancer. Major mutations of exon 19 deletion and exon 20 point mutation (L858R) are particularly well known in adenocarcinomas, and tyrosine kinase inhibitors (TKIs) have provided significant benefits to patients with such mutations. Complex mutation patterns of EGFR have also been reported, but their significance is unknown. Methods: Clinicopathological features and response to treatment of non-small lung cancer (NSCLC) with complex mutation of the EGFR gene were investigated in cases treated at Kanagawa Cardiovascular and Respiratory Center from June 2014 to March 2016. Results: EGFR gene analysis was performed in 334 cases, of which 108 had EGFR mutations. These cases included 7 (6.5%) with complex mutations: two males (28.6%) and five females (71.4%) with an age of 71.0±6.0 (mean±SD) years. Five of the 7 cases underwent surgery and two were inoperable. The histological diagnoses were adenocarcinomas (n=6) and squamous cell carcinoma (n=1). The pathological stage in the surgical cases (all adenocarcinomas) were IB, IIA, and IIIA in 2, 1, and 2 cases, respectively. Both inoperable cases were clinical stage IV. The EGFR complex mutation patterns were 19 deletion and 20 T790M (n=2, with one case with acquired TKI resistance), 18 G719X and 21 LB610 (n=3), 19 deletion and 21 L858R (n=1), and 20 T790 and 21 L858R (n=1). In the five surgical cases, two (pStage IIA, 19 deletion and 20 T790M, pStage IIIA, 18 G719X and 21 LB610) received postoperative TKI therapy because of recurrence. Both patients had a poor response to TKIs and both died. The patients in another three surgical cases are alive without receiving TKI therapy. Two inoperable cases (19 deletion and 20 T790M, 18 G719X and 21 LB610) were treated with standard chemotherapy and died. The disease-free survival period in the surgical cases was 53±21 days and the overall survival period in the case with postoperative recurrence and the inoperable cases was 810±563 days. The progression-free survival period in inoperable patients treated with TKIs was 101.5±90.6 days. Conclusion: In patients with EGFR mutation status, 6.5% have complex mutations, of which 85.7% are minor- or minor-on-major mutations. Lung cancer with complex mutation of EGFR tends to have a poorer response to TKIs compared to cases with a major single mutation.

Keywords: Epidermal growth factor receptor, Complex mutation, single mutation, non-small lung cancer.
P1.02-020 THE EFFECT OF EGF-PATHWAY TARGETED IMMUNIZATION (EGF PTI) ON STAT3 AND CANCER STEM CELLS IN EGFR MUTANT NSCLC CELLS

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Background: The vast majority of advanced non-small cell lung cancer (NSCLC) patients with EGFR mutant tumors will develop disease progression following successful treatment with an EGFR tyrosine kinase inhibitor (TKI). Resistance to EGFR-TKIs is due to various mechanisms, such as the secondary mutation (T790M) or the activation of alternative pathways (MET, AXL). What has not been fully appreciated is that EGFR blockade induces an imbalance in favor of survival, increases activity of STAT3 and enriches lung CSCs through Notch3-dependent signaling. EGF-PTI was designed to elicit an antibody response against EGF, in order to reduce EGFR receptor signaling and limit tumor growth. We have explored whether EGF PTI alone or in combination with EGFR TKIs may efficiently inhibit STAT3 and target CSCs. Methods: EGF PTI was provided by Bioven (Europe) Ltd. Gefitinib, erlotinib and the recently FDA-approved third-generation EGFR TKI, AZD9291 (osimertinib) were purchased from Selleck chemicals. Western blotting was used to assess the effect of the drugs on ERK, AKT and STAT3 phosphorylation and on Notch3 and PARP cleavage in EGFR (del19) mutant NSCLC PC9 cells and gefitinib-resistant PC9-GRA4 cells. PC9-GRA4 cells have been established in our lab and harbor the resistant T790M mutation (T790M+). The protein expression of AXL and CSC markers such as HES1 (downstream effector of Notch) and Bmi1 was also examined. Results: Gefitinib, erlotinib or AZD9291 suppressed EGFR, ERK1/2 and AKT phosphorylation in PC9 cells but increased STAT3 phosphorylation on the tyrosine residue 705 in both PC9 and PC9-GRA4 cells. EGF-PTI suppressed STAT3, EGFR and ERK1/2 and the combination of each of the three EGF TKIs with EGF-PTI induced more potent inhibition of STAT3, EGFR and ERK1/2. The EGF-PTI induced AKT phosphorylation was reversed when EGF-PTI was combined with EGFR TKIs. Interestingly, EGF-PTI blocked Notch cleavage and decreased the expression of HES1. The expression of Bmi1 and AXL were also attenuated with EGF PTI and apoptosis was enhanced through the induction of PARP cleavage. Conclusion: EGF-PTI may reverse mechanisms of resistance to single EGFR inhibition and the combination of EGF PTI with EGFR TKIs efficiently inhibits downstream signaling pathways in T790M+ cells. Based on these results, the design of a proof-of-concept trial with the combination of EGF PTI with gefitinib for the first line treatment of EGFR mutant NSCLC patients is in progress.

Keywords: non-small cell lung cancer, STAT3, Cancer Stem Cells, EGFR pathway targeted immunization

P1.02-022 ESTABLISHING REFLEX NGS TESTING IN NSCLC IN A REGIONAL NETWORK OF COUNTY HOSPITALS IN CENTRAL SWEDEN

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Background: Extended genetic testing of NSCLC tumor samples provides a foundation for personalized cancer treatment and use of new targeted medication. Testing with Next Generation Sequencing (NGS), mostly performed at university hospitals, has not been available for all patients due to geographic and economic reasons. Many lung cancer patients carry a heavy burden of disease and extensive travelling can negatively impact quality of life. The ability to perform a modern state-of-the-art work-up at local hospitals, without compromising on diagnostic quality, will enable equal access to personalized treatment for lung cancer patients. Methods: In Gaivle County hospital routine diagnostic immunohistochemistry (IHC) on biopsies is performed at the local pathology lab. In the case of NSCLC the formalin-fixed, paraffin embedded (FFPE) tissue samples are sent to Uppsala University hospital for further molecular pathology and NGS testing. A targeted NGS test (18 gene panel) was established for mutation screening of small biopsies and cytology specimens (Moens et al., J Mol Diagn, 2015). Fusion genes - ALK, ROS1 and RET - are analysed by IHC, FISH and nanoString. Structured biobanking of surplus biopsies and blood samples during treatment, for explorative biomarker testing and research, was set up as a regional extension of the UCAN infrastructure, including detailed registration of clinical baseline and real-time follow-up data in a dedicated database. Results: Inclusion of patients in the biobanking cohort started gradually during 2015 in Uppsala, and in February 2016 in Gaivle. The cumulative inclusion in the UCAN biobank is updated at www.u-can.uu.se (see Statistics). To date (July 2016) 70 patients have been included at Gaivle County hospital covering 95% of the newly diagnosed NSCLC patients. So far 242 patients from the region were tested by NGS yielding 23 EGFR+ (9.5%), 75 KRAs+ (31%), 5 BRAF+ (2%, codon 600), 2 MET (0.8%, exon 14 skipping), 1 ERBB2 (0.4%, exon 20 insertion), and 6 PIK3CA (2.5%, exon 9/20) cases. Fusion gene analysis resulted in 5 ALK+ (2%), 1 ROS1 and 1 RET patients. Conclusion: Decentralised local patient care, tissue/blood sampling and biobanking in combination with centralised molecular testing allows advanced lung cancer diagnostics and clinical research in networks of county hospitals. Survival benefits from modern targeted drugs, for national lung cancer cohorts, can only be achieved and evaluated in population-based settings without bias related to selective referral to major cancer centers.

Keywords: FFPE, next generation sequencing, NSCLC

Poster Session 1 - P1.02: Biology/Pathology - Driver Genes in NSCLC, Resistance, and Other - Monday, December 5, 2016

P1.02-021 REVIEW OF CLINICAL OUTCOMES ATTRIBUTABLE TO NEXT GENERATION SEQUENCING BASED BROAD MUTATION PANEL TESTING IN LUNG ADENOCARCINOMA

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Background: Molecular testing of lung cancer is currently performed on a relatively restricted standard of care genes (typically EGFR and ALK). The introduction of next generation sequencing (NGS) in clinical laboratories has permitted the adoption of broader testing using mutation panels. This study compared the number of mutations detected and outcomes generated as a result of replacing standalone EGFR and ALK assays with a combined mutation and gene fusion assay based on NGS in routine clinical practice.

Methods: Pathology testing was implemented using a bioinformatically selected subset of targets from the Thermo-Fisher Oncomine1 assay. The results of testing were compared against the incumbent assay platforms (Roche Cobas® EGFR, Abbott Vysis® ALK) to determine differences in mutation detection and resultant alterations to patient treatment. Results: Over a 5 month period of testing, 231 lung adenocarcinomas were analysed using the extended mutation and fusion panel. In total 126 of 231 cases had a mutation or fusion identified, EGFR (n=33), KRAS (n=76), BRAF (n=8), ERBB2 (n=2), ALK-fusion (n=5), RET fusion (n=1). Additionally, one off-target mutation was detected during assay QC. Of the above results 31 EGFR and 5 ALK would have been detected using the benchmark Roche Cobas EGFR and Abbott Vysis ALK FISH methodologies. The additional detections can be classified as nonactionable (KRAS, BRAF) or actionable (RET fusion, 2 EGFR mutations not identified by Cobas, 2 ERBB2 mutations and one off-target fusion). Of the 6 actionable genetic lesions, 4 selected for targeted therapies in lung cancer (EGFR, ERBB2). Two fusions detected by this assay (CCDC6-RET and TMPRSS2- ERG) suggested an alternative diagnosis to that of lung cancer when reviewed with morphology, immunohistochemistry and clinicopathological correlation. Conclusion: When compared with standalone assay testing, panel testing of lung cancer identified mutations in an additional 39% of patients and identified genetic lesions that offered targeted therapies. What has not been fully appreciated is that EGFR blockade induces an imbalance to subtype 39% more cancers and identifying an additional 2% of cases where targeted therapies may be of benefit. Crucially, the addition of ‘off-target’ mutations and fusions promotes re-examination and, where necessary, correction of primary diagnosis at a rate of 1% in our hands. This feature of panel testing has been overlooked and it is critical for the oncology and pathology communities to be aware of its significance.

Keywords: Molecular Pathology, EGFR, ALK

Poster Session 1 - P1.02: Biology/Pathology - Driver Genes in NSCLC, Resistance, and Other - Monday, December 5, 2016
P1.02-023 APPLICATION OF AN AMPION-BASED NGS STRATEGY IN THE MOLECULAR DIAGNOSIS OF NSCLC: COMPARABLE PERFORMANCE WITH FISH AND ARMS-PCR

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Background: Next generation sequencing (NGS) enables us to detect comprehensive genetic aberrations within a tumor sample, which provides potential therapeutic strategies to well adopted clinical diagnostic approaches such as amplification refractory mutation system PCR (ARMS-PCR) and FISH. However, there is no enough data to illustrate the overall concordance between NGS with traditional clinical diagnostic approaches. This study is aimed to fill in this blank. Methods: We have used 20 cell lines from ATCC and 19 FFPE samples to construct molecular standards and there are 50, 34 and 48 samples for SNV and InDel, CNV and fusion, respectively. All the mutations were verified by Sanger sequencing or QuantoStudio 3 digital PCR. To assess the performance of NGS, an ampion-based NGS strategy was used to detect gene mutations in molecular standards. In order to illustrate the overall concordance between NGS with ARMS-PCR and FISH, we further performed the RNA sequencing on 50 breast cancer patients. Results: So far, we have detected genetic aberrations in 108 FFPE samples. For SNV and InDel, we focused on the motif of EGFR, KRAS, BHD and PIK3CA, which were the most common mutations in NSCLC. In molecular standards, 34% of 50 (68%) were positive for Sanger and 33 of 50 were positive for NGS, thus the sensitivity, specificity and accuracy was 97%, 100% and 98%, respectively. In FFPE samples from 31 lung cancer patients, NGS results were consistent with ARMS-PCR. For CNV, in molecular standards, the copy number of HER2, MET, EGFR and FGF7 detected by NGS was high consistent with digital PCR and R2 was 0.9673. In FFPE samples from 45 breast cancer patients, 80% of cases (36/45) wereHER2 amplification positive and 20% (9/45) were negative for FISH, 34 HER2 positive and 9 HER2 negative for FISH were also classified by NGS. Thus, the overall concordance between NGS and ARMS-PCR and FISH was 95.56%. For CNV, the overall concordance were both 100% in 48 molecular standards (NGS versus Sanger sequencing) and 32 FFPE samples (NGS versus FISH). Conclusion: Our result reveal that the ampion-based NGS strategy for detecting genetic aberrations is of high accuracy and comparable with standard clinical diagnostic approaches, and therefore provides a promising diagnosis approach for clinical in the future.

Keywords: ampion-based next generation sequencing, genetic aberrations, clinical diagnosis

POSTER SESSION 1: Abstracts, Monday, December 5, 2016

P1.02-024 THE MOLECULAR BREAKDOWN: A COMPREHENSIVE LOOK AT NON–SMALL-CELL LUNG CANCER WITH ALK REARRANGEMENT

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Background: Chromosomal rearrangements of anaplastic lymphoma kinase (ALK) compose approximately 4–6% of non–small-cell lung cancer (NSCLC) and the patients can be prescribed with targeted therapy. Nevertheless, acquired resistance towards existing ALK-specific inhibitors is inevitable in most cases. This suggests that a detailed molecular characterization of NSCLC with ALK rearrangement and dissection of ALK-specific signaling pathway are strongly needed. Methods: Approximately 3000 NSCLC cases with EGFR and KRAS wild types were screened for ALK alterations by immunohistochemistry (IHC). From 1555 NSCLC IHC positive cases, we further validated ALK rearrangement through fluorescence in situ hybridization and RNA color-coded probes. We then performed targeted deep sequencing using a customized panel embedded with 81 select set of cancer associated genes in 129 ALK positive cases for their molecular characterization. Additional clinical analysis and drug viability assays between EML4-ALK long and short forms were assessed as well. We also conducted multiplexed direct mRNA expression profiling using a panel of 770 essential known genes that take part in most cancer pathways. Target gene silencing, overexpression, migration assay, and immunoprecipitation were conducted for functional analysis of identified molecules. Results: We found that most ALK genomic breaks occurred at intron 19 (92.7%), which conjointed with partner genes through non-homologous end joining repair system. ALK fusion profiling exhibited that 82% of fusions were EML4-ALK (129/158), 2.4% were HIPPI-ALK (4/158), 1.8% KIF5B-ALK (3/158), 1 case was KLTC1-ALK, and the rest were unrecognized ALK fusions (21/158). From the unknown partners, we identified 3 novel ALK fusion partners: GCC2, LM07, and PHACTR1. We also identified 4 novel somatic mutations of ALK: T1151R, R1192P, A1280V, and L1535Q, RNA expression profiling further revealed that NSCLC with ALK rearrangement showed higher expression of ITGB3 with statistical significance. Combinatorial treatment of ALK (crizotinib) and ITGB3 (LM609 antibody) decreased cell migration and invasive properties of ALK-positive colonies. Furthermore, from our new classification system of EML4-ALK variants, the cases with short EML4-ALK form showed more advanced stages and more frequent metastases than the cases with long form in NSCLCs. Conclusion: This is the primary mass-scale study of ALK-rearranged NSCLC to our knowledge. Through this integrated analysis, we provide genomic details and clinical insight of NSCLC with ALK rearrangement. Also, we suggest a novel therapeutic approach of treating ALK-rearranged NSCLC patients with ALK and ITGB3 inhibitors.

Keywords: Genomic landscape, ALK, ITGB3, NSCLC

POSTER SESSION 1: Abstracts, Monday, December 5, 2016

P1.02-025 EVALUATION OF NGS AND RT-PCR METHODS FOR ALK ASSESSMENT IN EUROPEAN NSCLC PATIENTS: RESULTS FROM THE ETOP LUNGSCAPE PROJECT

Stephen Finn1, Igor Letovanev2, Panagiota Zygoura3, Paul Smyth4, Alex Soltermann5, Lukas Bubendorf5, Ernst-Jan Speel6, Antonio Marchetti7, Daisuke Nonaka2, Kim Monkhorst2, Henrik Hagel7, Miguel Martorell7, Aleksandra Seja8, Richard Cawston8, Javier Hernandez4, Joungho Han1, John Vansteenkiste9, Spasenija Savic2, Jessica De Lorio10, Attilio Navarro11, Enriqueet Felip11, Arne Warth12, Peter Maagel13, Fionna Blackhall14, Marie-Dingembre15, Hendrik Dienemann16, Ralf Dzidzuszko17, Johan Vansteenkiste18, Thomas Geiger19, Jon Sherlock20, Jeffrey Schagem21, Urana Dafni21, Roswitha Kammler22, Keith Kerr23, Erik Thunnissen24, Solange Peters24, Rolf Stahel24, On Behalf Of The Etop Lungscape Consortium25

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Background: The reported prevalence of ALK rearrangement in NSCLC ranges from 2–7%, depending on population and detection method. The primary standard diagnostic method is fluorescence in situ hybridization (FISH). Recently, immunohistochemistry (IHC) has also proven to be
reproducible and sensitive technique. Reverse transcriptase-polymerase chain reaction (RT-PCR) has been advocated and most recently the advent of Targeted Next-Generation Sequencing (NGS) for ALK and other fusions has become possible. This one of the first studies comparing all 4 techniques in resected NSCLC from the large ETOP Lungscape cohort. Methods: 96 cases from the ETOP Lungscape (Iobank N=2709) selected based on any degree of IHC staining (clone 5A4 antibody, Novoceastra, UK) were examined by FISH (AAbbott Molecular, Inc., Blacklath, JCO 2014), central RT-PCR and NGS. High 120 clones were sifted off for IHC. For both RT-PCR and NGS, RNA was extracted from the same formalin-fixed, paraffin-embedded tissues. For RT-PCR, primers were used covering the most frequent ALK translocations. For NGS, the Oncomine™ Solid Tumour Fusion Transcript Kit was used, allowing simultaneous sequencing of 70 ALK, RET and ROS1 specific fusion transcripts associated with NSCLC, as well as 6 novel ALK translocations using 5'-3' ALK gene expression ‘Imbalance Assay’. Results: NGS provided results for 90 cases, while RT-PCR for 77. Overall, 70 cases have results for all 4 methods, with fully concordant 60 (85.7%) cases (40 ALK, 11 ALKt). Before employing the ‘Imbalance Assay’, in 5 of the remaining 10 cases, NGS differs from the other methods (3 NGS vs 1 NGS), while in the other 5, NGS agrees with RT-PCR in all, IHC in 2, and FISH in 1. Using the concordant result of at least two of the three methods as true negative/positive, the specificity and sensitivity of the fourth is 96/94/100/96% and 94/94/89/72% for IHC/FISH/RT-PCR/NGS, respectively (incorporating imbalance; NGS sensitivity=83%). Imbalance scores are presented here for 19 NGS cases: 5 ‘NGS-/FISH+/IHC-', 9 'NGS-/FISH-/IHC-', and 5 'NGS-/FISH+/IHC+' (Figure S1). There is strong evidence for imbalance in 4 cases (score's range: 0.0144-0.0555), uncertain in 5 (range: 0.0030-0.0087), and no evidence (score's range: 0.0004) in the 9 negative cases. Conclusion: NGS is a useful screening tool for ALK rearrangement status, superior to RT-PCR when RNA yield is limited. When using NGS, it is critically important to integrate the 5'-3' imbalance assay and to confirm with one or more additional methods in the ‘imbalance’ cases. Data further highlight the possibility of missing actionable rearrangements when only one screening methodology is available.

Keywords: ALK, NGS, ETOP, Lungscape

P1.02-026 DETECTION OF LOW-ABUNDANT EGFR SOMATIC MUTATIONS BY PNA CLAMPING-ASSISTED FLUORESCENCE MELTING CURVE ANALYSIS
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Background: Detecting mutations is becoming important for both predicting disease progression and drug responses to treatment of cancer patients. Currently, mutation detection methods for cancer diagnosis are mainly based on the invasive sampling technique such as a tissue biopsy, but some patients may not available for this invasive procedure. Therefore, circulating tumor DNA (ctDNA) would be a good alternative for those patients. However, testing methods for tissue biopsy sample are not applicable to ctDNA samples due to relatively lower sensitivity. A highly sensitive assay method is required for detecting mutations in liquid biopsy samples. Methods: We have developed a highly sensitive and simple method to detect somatic mutation from ctDNA in patient's plasma. This new real-time PCR-based testing method (PANAMutyper™) has maximized unique properties of peptide nucleic acid (PNA). It contains a PNA clamp and PNA detection probes in the each DNA sequences, and then suppress amplification during the PCR reaction. Meanwhile, a PNA detection probe that conjugated with a fluorescent dye (PANAMutyper™) has maximized unique properties of peptide nucleic acid (PNA). It contains a PNA clamp and PNA detection probes in the each DNA sequences, and then suppress amplification during the PCR reaction.

Results: In order to confirm the validity in real condition, we conducted spiking test. Ten of mutant clones DNA were used as standard materials. (G719A, G719S, G719S, S768I, Exon19 deletion, T790M, 1469DelG, L858R, E926A, L861Q). In the each mutant DNA, 1000 copies were used as positive controls. 1000 copies were used as negative controls. 1000 copies were used for microtiter concentration. And then we extracted ctDNA from prepared sample. As a result, all of ten mutant DNA was detected 1 copy/μl. This result suggest that PANAMutyper™ is applicable to ctDNA derived from patient’s plasma sample. Conclusion: The high concordance, specificity, and sensitivity of this test have demonstrated that EGFR mutation status can be accurately assessed by PANAMutyper™ using ctDNA. Therefore, PANAMutyper™ can be used in various clinical areas including companion diagnostics and monitoring acquired mutations.

Keywords: EGFR, Circulating Tumor DNA, PNA, Melting curve analysis

P1.02-027 A COMPARATIVE ANALYSIS OF DIFFERENT CYTOLOGICAL SAMPLES FOR THE ASSESSMENT OF ALK GENE REARRANGEMENTS IN NSCLC PATIENTS
Maria Lozano Escario1, Luis Mejias1, Marta Abengozar2, Tania Labiano1, Jose Subitl, Alfonso Gurpidé3, Mercedes Aguirre1, Nerea Gomez1, Maria Eugenia Echarri1, M Amada Maset1, Jorge Arabe1, Pablo Panadero1, Jose Paricio1, Miguel Idoate1, Jose Echeveste1
1Pathology, University of Navarra, Pamplona/Spain, 2Pathology, Hospital de Navarra, Pamplona/Spain, Gastroenterology, University of Navarra, Pamplona/Spain, 3Medical Oncology, University of Navarra, Pamplona/Spain

Background: Determination of ALK gene rearrangements has been traditionally performed in biopsies and/or surgical specimens. However, advanced lung cancer is often diagnosed by FNA cytology obtained through minimally invasive procedures, and frequently cytological specimens are the only samples available, thus emphasizing the necessity to expand ALK analysis to cytologic specimens. We assessed the feasibility of determining ALK gene rearrangements in different types of cytological specimens. Methods: We studied prospectively 268 cytological samples from 268 NSCLC patients for ALK gene rearrangements by FISH (Vysis LSI ALK Dual Color Break Apart and Zytography SPEC ALK Dual Color Break Apart). Tumour samples were obtained by bronchoscopy (169 cases), transthoracic needle aspiration (22 cases), transthoracic biopsies (15 cases), and pleural fluids (9 cases). The nuclei on cytology smears are not truncated, which allows for the detection of the true number of FISH signals in a nucleus. It is mandatory an exquisite management and care of the samples to preserve the material for FISH analysis. Fifteen cases (5.59%) had ALK rearrangements. One case had a concurrent EGFTR mutation in exon 21 plus the T799M mutation, and two had also KRAS mutations (G12D and G12C respectively). FISH study was unsuccessful in 33 cases (12.3%). 8 from stained smears (6.01%), 12 from ThinPrep (25%), 8 from SurePath (66.6%). Correlation cytological/paraffin embedded samples was performed in 10 cases with a concordance rate of 100%. Conclusion: ALK gene rearrangements may be definitely detected in cytological samples and particularly in direct smears. Both Papanicolaou and Diff-Quick smears are suitable samples for FISH analysis. The nuclei on cytology smears are not truncated, which allows for the detection of the true number of FISH signals in a nucleus. It is mandatory an exquisite management and care of the samples to preserve quality. Coexistence of ALK gene rearrangements and EGFR and KRAS mutations were observed in one case (6.01%), indicating that such alterations are not necessarily mutually exclusive.

Keywords: ALK, cytology, FISH, Smears

P1.02-028 DETECTION OF Oncogenic DRIVERS in PLEURAL EFFUSIONS and ARCHIVED FNA SMEARS of PULMONARY ADENOCARCINOMA
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Background: Determination of ALK gene rearrangements has been traditionally performed in biopsies and/or surgical specimens. However, advanced lung cancer is often diagnosed by FNA cytology obtained through minimally invasive procedures, and frequently cytological specimens are the only samples available, thus emphasizing the necessity to expand ALK analysis to cytologic specimens. We assessed the feasibility of determining ALK gene rearrangements in different types of cytological specimens. Methods: We studied prospectively 268 cytological samples from 268 NSCLC patients for ALK gene rearrangements by FISH (Vysis LSI ALK Dual Color Break Apart and Zytography SPEC ALK Dual Color Break Apart). Tumour samples were obtained by bronchoscopy (169 cases), transthoracic needle aspiration (22 cases), transthoracic biopsies (15 cases), and pleural fluids (9 cases). The nuclei on cytology smears are not truncated, which allows for the detection of the true number of FISH signals in a nucleus. It is mandatory an exquisite management and care of the samples to preserve quality. Coexistence of ALK gene rearrangements and EGFR and KRAS mutations were observed in one case (6.01%), indicating that such alterations are not necessarily mutually exclusive.

Keywords: ALK, cytology, FISH, Smears
Table 1: Summary of mutation analysis

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<th>Gene</th>
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Conclusion: These findings verify the feasibility of analysis of oncogenic drivers in cytological specimens in advanced ADC. Stained aspiration smears can be used after establishing diagnosis and checking adequacy of the specimen.

Keywords: oncogenic Drivers, pulmonary adenocarcinoma, pleural effusions, FNA smear.

P1.02-030 PERFORMANCE EVALUATION OF ALK/ROS1 DUAL BREAK APART FISH PROBE KIT (RUO) IN NON-SMALL-CELL LUNG CANCER

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Background: ALK and ROS1 gene rearrangements are distinct molecular subsets of non-small-cell lung cancer (NSCLC), and they are strong predictive biomarkers of response to ALK/ROS1 inhibitors, such as crizotinib. Thus, it is clinically important to detect patients who will benefit from such treatment and develop an effective screening strategy. In this study, we aim to evaluate the diagnostic performance of ALK/ROS1 RUO FISH probes which can concurrently detect ALK and ROS1 rearrangements. Methods: The study populations were composed of three patient cohorts with histologically confirmed lung adenocarcinoma (ALK rearrangement, ROS1 rearrangement and both wild type). Patient specimens consisted of 12 ALK-positive, 9 ROS1-positive and 21 ALK/ROS1-wild type formalin-fixed paraffin-embedded samples obtained from surgical resection or excisional biopsy. ALK rearrangement status was determined by Vysis LSI Dual Color Break Apart Rearrangement Probe (Abbott Molecular, Abbott Park, IL, USA) and ROS1 rearrangement status was assessed by Zytolight SPEC ROS1 dual color break apart probe (Zytovision, Bremerhaven, Germany). All specimens were re-evaluated by ALK/ROS1 Break Apart FISH RUO 4-color kit. FISH images were scanned via the BioView Duet and interpreted remotely via BioView SoloWeb. Results: A total of 42 patient samples were evaluated. The concordance of results obtained from ALK/ROS1 Break Apart FISH RUO 4-color kit was evaluated relative to the ALK and ROS1 rearrangement status of the specimen, as previously determined. One ROS1-positive and 2 wild-type samples were excluded from analysis due to high background. Regarding ALK-positive samples, 12 were ALK-positive by ALK/ROS1 RUO FISH, showing 100% (n=12/12) sensitivity to predict ALK rearrangement. Regarding 8 ROS1-positive samples, 5 cases were ROS1-positive by ALK/ROS1 RUO FISH, showing 75% (n=6/8) sensitivity to predict ROS1 rearrangement. Two cases had weak ROS1 signals that could not be enumerated. Regarding 9 wild-type cases, 18 cases were negative by ALK/ROS1 RUO FISH, showing 95% (n=18/19) specificity, while one case showed poor ROS1 signals which could not be properly enumerated. Conclusion: ALK/ROS1 RUO FISH can detect ALK and ROS1 rearrangements simultaneously in NSCLC. The fluorescence of ROS1 signal may be weakened by slide shipment and remote scoring.

Keywords: ALK, ROS1, fluororescent in situ hybridization, non-small-cell lung cancer.
LUNG CANCER PATIENTS WITH EGFR-TKI RESISTANCE

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Background: Histomorphologic changes are known to be associated with the acquired resistance of the epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKI) treatment. Rebiopsy is usually used to detect the underlying molecular mechanism of resistance, however meticulous histologic examination is very important to identify the change of cancer phenotype. Here we tried to investigate histomorphologic changes between the initial and rebiopsy specimens. Methods: We retrospectively evaluated the initial biopsy and rebiopsy specimens of 60 patients with acquired resistance to EGFR-TKI between 2010 and 2016 in Seoul National University Bundang Hospital, Republic of Korea. EGFR mutation tests were performed in all specimens. Various histologic parameters including spindle cell components, discohesive growth pattern and stromal change, subtype of the tumor and nuclear grade were evaluated. In addition, immunohistochemistry (IHC) for epithelial-mesenchymal transition (EMT) markers (E-cadherin and vimentin) and neuroendocrine markers (CD56 and synaptophysin) was performed. Results: In rebiopsy specimens, 18 cases (30%) showed changes of cellular morphology including spindle cell components and discohesive growth pattern representing EMT features. On IHC, acquisition of vimentin expression in spindle cell components and decreased expression of E-cadherin in adenocarcinoma of rebiopsy specimens were identified. Furthermore, histologic transformation to small cell carcinoma (2 cases, 3.3%) with expression of neuroendocrine markers and squamous differentiation (2 cases, 3.3%) were observed. Conclusion: In this study, histologic transformation to EMT is the most frequent finding in rebiopsy samples of the patients with EGFR-TKI resistance while small cell carcinoma has been known to be the most common in the literatures. Although EMT has been reported to be about 5% of EGFR-TKI resistance, we observed it in approximately 30% of our rebiopsy cases. These findings suggest that detailed and meticulous pathologic evaluation plays an important role to find delicate histomorphologic changes associated with EGFR-TKI resistance.

Keywords: lung cancer, EGFR TKI, Resistance, epithelial-mesenchymal transition
83.3% of all patients with lung cancer and adenocarcinoma in Denmark are tested for EGFR mutations and 9.4% are positive. 73.1% of adenocarcinomas are tested for ALK translocations and 1.4% is found to be positive. In total only 8.8% of all tested lung cancer patients are found to be EGFR mutated and 1.3% has an ALK translocation. Conclusion: Data from primarily Asian lung cancer populations have shown significant higher rates of EGFR mutations and ALK translocations that the findings in this Danish population. Based on these data the cost-effectiveness of the chosen strategy for reflex testing lung cancer patients up front should be reconsidered.

Keywords: ALK translocations, lung cancer, EGFR mutations

Poster Session 1: P1.02: Biology/Pathology Driver Genes in NSCLC, Resistance, and Other - Monday, December 5, 2016

P1.02-035 Concomitant Driver Mutation Determines Tumor Growth in EGFR Mutation-Positive Lung Adenocarcinoma

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Background: In the practice of precision medicine, understanding tumor characteristics in the individual patient is crucial. The aim of this study was to analyze tumor aggressiveness from two perspectives: actual growth rate calculated from the tumor, and molecular profile obtained by next-generation sequencing. Methods: Participants comprised patients who underwent preoperative CT two or more times. DNA and RNA of 10 lung adenocarcinoma tumor samples were extracted. Whole-exome and -transcriptome data were obtained, and somatic mutations were detected. Preoperative CT scans were retrospectively reviewed and volume doubling time (VDT) of each tumor was calculated using a modified Schwarz equation. Results: Median VDT was 104 days (range, 42-653 days). All patients with somatic missense mutations were in 6 patients. Patients were divided into two groups by VDT for further analyses: Slow group with VDT >104 days (n=3); and Rapid Group with VDT <104 days (n=5). All patients with EGFR mutation without concomitant KRAS mutation were in the Slow Group. In contrast, a patient with concomitant mutations of EGFR and KRAS showed a considerably rapid growing tumor with a VDT of 45 days. Patient with concomitant mutations in EGFR and PIK3CA had a relatively slow-growing tumor, although VDT was the shortest in the Slow Group (120 days).

Conclusion: EGFR mutation was associated with slow growth of the tumor, although the growth rate may be influenced by concomitant mutation of other driver genes. This may be one of the reasons that the clinical response of tyrosine kinase inhibitors are poor in some patients with EGFR mutation. Assessment of tumor aggressiveness by molecular profiling and by sequential CT are both important for the practice of precision medicine.

Keywords: EGFR mutation, Volume doubling time, next-generation sequencing, Concomitant driver mutation

Poster Session 1: P1.02: Biology/Pathology Driver Genes in NSCLC, Resistance, and Other - Monday, December 5, 2016

P1.02-037 Mutations of EGFR and KRAS Genes in Belorussian Patients with Non-Small Cell Lung Cancer

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Background: Mutations of the epidermal growth factor receptor (EGFR) cause increased activation of EGFR and sensitivity of patients with non-small cell lung cancer (NSCLC) to tyrosine kinase inhibitors (TKIs). The effectiveness of TKIs depends on the presence of EGFR mutations, in particular EGFR L858R point mutation and T790M or exon 20 insertion. Recent data have shown that EGFR gene has other driver mutations in addition to classical EGFR mutations. This study was designed to determine the frequency of mutations in the EGFR and KRAS genes in Belarusian NSCLC patients.

Methods: Tumor samples were obtained from 107 patients with advanced NSCLC and were subjected to molecular analyses. After obtaining informed consent, formalin-fixed paraffin-embedded tissue samples were collected from the patients. DNA was extracted from tumor tissue using a QIAamp DNA FFPE Tissue kit. The EGFR and KRAS genes were screened for mutations in their exons 18, 19, 20, and 21. The qPCR was performed using the primers for the specific exons. Mutations were confirmed by Sanger sequencing.

Results: A total of 107 patients were included in the study, of whom 60 were males and 47 were females. The median age was 67 years (range 30-85). EGFR mutations were found in 31 patients (29.0%), with L858R being the most common mutation (27 patients, 25.2%). KRAS mutations were found in 28 patients (26.0%), with codon 12 mutations being the most common (20 patients, 18.7%). The remaining patients had no mutations in the EGFR and KRAS genes.

Conclusion: The frequency of EGFR mutations in this study was lower compared to other studies. The frequency of KRAS mutations was higher than that reported in other studies. These results suggest that the frequency of EGFR and KRAS mutations in Belarusian NSCLC patients may be different from that in other populations. Further studies are needed to determine the role of these mutations in the clinical outcome of NSCLC patients in Belarus.
among 3.3% of patients.

Analysis of mutations in exon 2 KRAS gene detected 3 types of mutations: p.G12D (1.03%), p.G12C (2.06%) and p.G13C (1.03%). The frequency of all mutations was 4.1% in the total group of patients. The mutations were found only in tumor tissues of men. 75% of mutations carriers are smokers. Analysis of KRAS mutations in association with the development of a specific histological type of lung cancer showed that mutations are more common in patients with AC (5.9%) than in patients with SCC (2.2%). Conclusion: Thus, in the researched group of patients mutations in the EGFR gene were found only among non-smoking women with AC, mutations in the EGFR gene were detected only among men independently of histological type of NSCLC.

Keywords: Epidermal growth factor receptor, mutations, non-small cell lung cancer

POSTER SESSION 1 - P1.02: BIOLOGY/PATHOLOGY
DRIVER GENES IN NSCLC, RESISTANCE, AND OTHER – MONDAY, DECEMBER 5, 2016

P1.02-038 OVER-EXPRESSION OF EPIDERMAL GROWTH FACTOR RECEPTOR 1 (EGFR) GENE IN SERUM OF ADENOCARCINOMA LUNG AT A TERTIARY CENTER IN NORTH INDIA
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Background: Epidermal growth factor receptor (EGFR) is a cell surface protein that binds to epidermal growth factor. Over expression of EGFR in tumor tissue has been observed in up to 65% of advanced non small cell lung cancer, and has shown promising prognostic potential. In this study, we compared the EGFR gene expression in serum adenocarcinoma lung with healthy controls. Methods: We analyzed 61 newly diagnosed patients of adenocarcinoma lung and 50 healthy controls. RNA was isolated from blood serum of all subjects and real time PCR (RT-PCR) was performed after complementary DNA (cDNA) synthesis. The level of EGFR expression in serum was calculated by relative quantification method and expressed as fold-increase compared to controls. Expression levels were also correlated with various clinico-pathological parameters. Results: Out of 61 patients, 42 were males. The mean (SD) age of the entire group was 54.5 (11.5) years. Most of the patients (79%) had stage IV disease. 23 (38%) patients were current/ex-smokers, with median pack years of 10 (range, 0.5-100). Majority of patients had KPS of 90 (51%) and ECOG 1 (74%) respectively. Activating mutations in EGFR were observed in the tissue of 14 (21.3%) of 61 patients; of these, 9 were exon-19 deletions and 6 were exon-21 point mutations. In the patients, a 19.66 mean-fold increase in serum EGFR gene expression was observed compared to healthy controls. No significant association was found between EGFR expression and other variables i.e., sex, age, smoking habit, performance status, stage of disease and EGFR mutation status. Conclusion: Serum EGFR gene was over expressed by >16 fold in advanced adenocarcinoma lung compared to healthy controls. The association of EGFR expression with other clinical disease characteristics needs further exploration.

Keywords: EGFR expression, RT-PCR, adenocarcinoma lung

POSTER SESSION 1 - P1.02: BIOLOGY/PATHOLOGY
DRIVER GENES IN NSCLC, RESISTANCE, AND OTHER – MONDAY, DECEMBER 5, 2016

P1.02-039 ASSESSMENT OF KRAS MUTATIONS (BY DIGITAL PCR) IN CIRCULATING TUMORAL DNA FROM LUNG ADENOCARCINOMA PATIENTS
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Background: KRAS mutations are detected in approximately 25% of lung adenocarcinoma (LA). Targeted therapies against KRAS are under investigation. The use of tumor biopsy for molecular testing may be challenging due to the invasiveness of the procedure, the limited material for multiple biomarker analyses and tumor heterogeneity. Mutation detection in circulating cell-free tumor DNA (ctDNA) can overcome these caveats and also be used for tracking tumor dynamics. The aim of this study was to evaluate KRAS mutation detection in plasma samples from LA. Methods: Plasma samples from 35 patients with histologically confirmed KRAS mutant LA were collected at initiation of chemotherapy. KRAS mutations were assessed using digital PCR technology (QuantStudio3D Digital PCR System, ThermoFisher Scientific). Correlation between ctDNA and tumor biopsies in terms of mutation detection was analysed. In 5 cases plasma samples were obtained during the course of the disease to monitor clonal dynamics. Results: Most cases were male (71%), with stage IV disease (83%), and showed KRAS mutation on codon12 (94%). KRAS mutation was found in plasma samples in 28/35 cases, showing a concordance with the tumor of 80%. In patients whose disease was limited to thorax (stages I, II and III, and IVA) KRAS mutation was detected in 7/10 (70%) plasma samples. Plasma/tumor biopsy concordance in cases with extra-thoracic metastases was 84% (21/25). The false negative cases had low burden of extra-thoracic disease, with bone (2 cases), brain (1 case), and abdominal lymph node (1 case) as the only metastatic location outside the thorax. KRAS clonal dynamics in plasma showed a good correlation with treatment responses in some cases (figure 1).

Conclusion: High concordance in the detection of KRAS mutations was found between plasma and tumor tissue using digital PCR technology, particularly in cases with extra-thoracic disease. Digital PCR allows for tracking clonal dynamics in KRAS mutant LA.

Keywords: liquid biopsy, KRAS, Clonal dynamics, lung adenocarcinoma

POSTER SESSION 1 - P1.02: BIOLOGY/PATHOLOGY
DRIVER GENES IN NSCLC, RESISTANCE, AND OTHER – MONDAY, DECEMBER 5, 2016

P1.02-040 HETEROGENEITY OF THE EGFR / KRAS GENE MUTATION IN MULTIFOCAL LUNG ADENOCARCINOMA AND THE CLINICAL SIGNIFICANCE
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Background: Significant advances on EGFR-targeted therapy have allowed increasing availability of therapeutic options for non small cell lung cancers. For multifocal lung adenocarcinoma patients in clinic, the EGFR gene mutation is generally examined only on the largest tumor or the one containing the most tumor cells, which could omit the tumors harboring the EGFR of mutation and thus loss of opportunity for the tyrosine kinase inhibitors therapy. Methods: A total of 58 cases of multifocal lung adenocarcinoma, including 129 intrapulmonary tumors resected surgically, was recruited for this study. The genome DNA samples were prepared from formalin-fixed and paraffin-embedded tumor tissues. The EGFR / KRAS mutational status of each tumor was examined by Sanger’s DNA sequencing. The targeted hotspot mutations in EGFR gene included p.G719S/C/A (exon 18, p.T790M(exon 20), p.L858R(exon 20), p.L858R (exon 21), p.L861Q (exon 21) and deletions in exon 19. The hotspot mutations in KRAS genes were within codon 12 including p.G12C or p.G12A mutation. Results: In this group of 58 patients with multifocal lung adenocarcinoma, 38 patients were found EGFR or KRAS mutations in their tumors. Among them, the EGFR mutations were detected in 59 tumors derived from 34 cases; while the KRAS mutations were detected in 7 tumors from 5 cases. One patient (Case 30) was identified EGFR(exon 18, p.G719A) or KRAS (p.G12A or p.G12C) mutation in her 3 tumors, respectively.
It is noteworthy that there were 21 (36.2%) in the 58 cases showing the mutational heterogeneity among the multiple intrapulmonary tumors derived from one individual, and that 6 tumors harbored 2 different types of EGFR mutation. However, none of the specimens investigated contained both EGFR and KRAS mutations within a same tumor. Comparing data from the present study along with the molecular pathological diagnosis records from the Department of Pathology, among the 58 cases enrolled, 30 cases accepted routine molecular pathological examination to check the EGFR / KRAS mutation, and 28 cases did not. However, 37 out of 66 tumors from the 30 cases were tested – only 5 patients had all their tumors examined, whereas in the rest total 92 tumors unchecked, 42 EGFR sensitive mutations were identified in this study. Conclusion: Current finding suggests that the EGFR and KRAS mutational heterogeneity is widely existed in multifocal lung adenocarcinomas. Therefore, reliable and exhaustive examination for EGFR / KRAS mutation should be executed in the every tumor, to provide more individualized therapy choices for the patients.

Keywords: Heterogeneity, multifocal lung adenocarcinoma, EGFR gene mutation

**Poster Session 1: PI.02: Biology/Pathology Driver Genes in NSCLC, Resistance, and Other – Monday, December 5, 2016**

**P1.02-041 CHARACTERIZATION OF MET-N375S AS AN ACTIVATING MUTATION IN SQUAMOUS CELL CARCINOMA OF THE LUNG**

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Background: Over the years, significant progress has been made in the treatment of lung carcinoma. While targeting EGFR mutations and the epidermal growth factor receptor (EGFR) pathway have yielded impressive therapeutic gains in lung adenocarcinoma, the rarity of genetic aberration in squamous cell carcinoma (SCC) has restricted the use of molecular-targeting agents. Next-Generation sequencing analysis has identified a high frequency of c-MET mutations in Asian lung SCC specimens, in particular the N375S (MET-N375S) mutant. This study aims to characterize the functional significance and therapeutic implications of MET-N375S in lung SCC cells. Methods: MET (N375S) mutation in tumour tissues was verified with droplet digital PCR. c-MET mutant expressing clones were generated through site-directed mutagenesis and single cell clonal selection. The impact of MET-N375S in lung SCC cells was characterized by defining the downstream effectors (Proteome profiling), biological functions (anchorage-independent growth, invasion and migration assays), transcrptional regulation (RNAseq) and protein-protein interaction (SLAC). Novel binding partners of MET-N375S was verified using co-immunoprecipitation (co-IP) and proximity ligation assay (PLA). Sensitivity of c-MET mutant to various kinase inhibitors was determined with CellTiter-Glo assay. Results: MET(N375S) mutation was confirmed in 9/45 lung SCC specimens (20%). Ectopic expression of MET-N375S in lung SCC cells significantly elevated the activation of downstream Src, p38 and ERK1/2 kinases, increased phosphorylation of c-Met and p42/44 MAPK, and anchorage-independent colony forming ability in vitro. Despite so, comparative transcriptomic analysis revealed that epithelial-mesenchymal signature genes were not induced in cells expressing mutant c-MET. On the contrary, SLAC and co-IP analyses on the MET-N375S interactome demonstrated an increase in binding affinity towards receptor tyrosine kinases (RTKs) as compared to wild type c-MET, which was confirmed with in situ PLA. Moreover, MET-N375S augmented in vitro sensitivity to selective MET inhibitors. Conclusion: These findings suggest the role of MET-N375S as an activating mutation that strongly enhance malignant transformation and metastatic potential in lung SCC cells. Mechanistically, the dysregulation of various oncogenic events could be associated with the formation of heterodimers with RTKs. Clinically, MET-N375S could be utilized as a potential predictive biomarker for patients with advanced SCC of the lung to be treated with selective MET inhibitors.

Keywords: Lung Squamous cell carcinoma, c-MET mutation

**P1.02-043 MULTIPLEXED FISH (ALK/ROS1, RET, NTRK1) IN LUNG ADENOCARCINOMAS: NOVEL DUAL ALK/ROS1 PROBE AND AUTOMATED SCANNING SYSTEM**

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Background: Although the use of NGS (next-generation sequencing) is indeed feasible for the study of druggable rearrangements, the sensitivity and specificity of targeted NGS has been challenged on several grounds: use of fixed tissue, poor quality/insufficient sample, RNA-contamination risk and long turn-around time. Our relatively high rate of failures (7.6%) with the NGS analysis represents the limiting factor for many laboratories. The NGS results confirmed the FISH findings. Conclusion: Simultaneous FISH was performed in a series of consecutive cases from Northeastern Brazil, a previously untested population, and correlated with histologic subtypes according to the 2015 WHO Classification. Results: A total of 94 patients (55% female, mean age 62 years) were tested, including 51 solid, 29 acinar, 6 lepidic, 6 papillary predominant and 2 sarcomatoid carcinomas with adenocarcinoma components. There were 9 positive cases (9.5%), 5 solid predominant, 3 acinar predominant and 1 lepidic. One of the 3 acinar cases had a mucinous component. The positive cases were more often male (p<0.05) with no significant differences in relation to age, smoking history or histologic subtype. The negative cases showed a 32% EGFR mutation rate. Follow-up will be presented. Conclusion: We will describe a series of consecutive adenocarcinomas from a population with unknown ALK status with a higher than expected rates, and correlate with the 2015 WHO Classification of Tumors.

Keywords: Adenocarcinoma, ALK, biomarker, Latin America

**Poster Session 1: PI.02: Biology/Pathology Driver Genes in NSCLC, Resistance, and Other – Monday, December 6, 2016**

**P1.02-042 DETECTION OF ALK PROTEIN EXPRESSION IN LUNG ADENOCARCINOMAS, A CONSECUTIVE SERIES OF CASES FROM NORTHEASTERN BRAZIL**

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Background. There have been very few studies on ALK status in lung adenocarcinomas in Latin American population. No prior reports in Northeastern Brazil have been published. Methods: We analyzed ALK protein expression with a specific antibody (DS53 clone) with the Ventana system in a series of consecutive cases from Northeastern Brazil, a previously untested population, and correlated with histologic subtypes according to the 2015 WHO Classification. Results: A total of 94 patients (55% female, mean age 62 years) were tested, including 51 solid, 29 acinar, 6 lepidic, 6 papillary predominant and 2 sarcomatoid carcinomas with adenocarcinoma components. There were 9 positive cases (9.5%), 5 solid predominant, 3 acinar predominant and 1 lepidic. One of the 3 acinar cases had a mucinous component. The positive cases were more often male (p<0.05) with no significant differences in relation to age, smoking history or histologic subtype. The negative cases showed a 32% EGFR mutation rate. Follow-up will be presented. Conclusion: We will describe a series of consecutive adenocarcinomas from a population with unknown ALK status with a higher than expected rates, and correlate with the 2015 WHO Classification of Tumors.

Keywords: ALK, NTRK1, ROS1, FISH
Background: There is limited Brazilian data on epidermal growth factor receptor (EGFR) gene activating mutations prevalence and their clinicopathologic associations especially in the Northeast, with no previous epidemiologic report. The current study aimed to assess the relationship between EGFR mutations and histologic subtypes according to the 2015 WHO Classification. Methods: We assessed the frequencies of EGFR mutations in consecutive pulmonary adenocarcinomas among a population-based sample in Northeastern Brazil. A sample of 351 patients diagnosed from 2014-2016 was analyzed by direct sequencing (45.5%), real time PCR (34.1%) or next generation sequencing (20.4%). Results: The overall mutation rate was 30.5%. The ratio of exon 19 deletions to exon 21 L858R mutations was 1.2:1. Three patients had T790M mutations detected after progression in first line of targeted therapy. Female sex (P = 0.002), never-smoking status (P = 0.002), and nonsolid subtype of ADC (P = 0.001) were associated with significant when evaluated solely. Papillary component did not show correlation to mutations. Tumor differentiation correlated significantly with their incidence of EGFR mutations, lower in poorly differentiated tumors (p=0.005). Follow-up will be presented. Conclusion: We will describe a series of consecutive adenocarcinomas from a population with unknown status with a higher than expected rates (higher than Southern Brazil and similar to other Latin American countries), and correlate with the 2015 WHO classification of tumors.

Keywords: EGFR, lung adenocarcinoma, Latin America

POSTER SESSION 1 - P1.02: BIOLOGY/PATHOLOGY
DRIVER GENES IN NSCLC, RESISTANCE, AND OTHER – MONDAY, DECEMBER 5, 2016

P1.02-046 ALK IHC IS HIGHLY SENSITIVE TO FIXATION PARAMETERS
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Background: An ALK genetic translocation event occurs in ~2-7% of non-small cell lung carcinoma patients (NSCLC), resulting in the constitutive expression of an active chimeric ALK protein, which leads to tumor proliferation. Ventana has developed a fully automated immunohistochemistry (IHC) assay using the VENTANA anti-ALK (DSF3) Rabbit Monoclonal Primary Antibody (ALK (DSF3)) to detect the ALK protein in formalin fixed paraffin embedded tissue. ALK IHC testing is becoming more widespread in NSCLC, however, information concerning the impact of previous fixation conditions when testing limited. We used human cell lines expressing ALK, generated as xenografts to evaluate the effect of Fixation Type, Time, and Delay to Fixation (Isciehima) on the ALK antigen as measured by the ALK (DSF3) antibody staining intensity. Methods: NCI-H2228 human NSCLC cell lines were used to generate xenograft tumors in SCID mice. In order to assess Isciehima (delay to fixation) H2228 xenografts were used to model Isciehima in 10% NB. The impact of fixation on staining performance of the ALK (DSF3) primary antibody was assessed using the H2228 xenografts to model fixation type and fixation time for 10% NB, Zinc Formalin, 35% Alcohol, Alcoholic Formalin Acid, BS, and Prefer for 1, 6, 12, 24 and 72 hours. Each of the stained slides were evaluated by a pathologist using a qualitative assessment and scored on a 0-3+ intensity scale (0 = no staining detected, 1+ = weak staining detected, 2+ = moderate staining detected, 3+ = strong staining detected). Results: Fixation in all time points in BS, Prefer, and AFA, as well as ethanol, severely compromised staining intensity of ALK (by decreasing staining intensity greater than 0.5 points). Iscicemia greater than 6 hours also decreased staining intensity. In contrast, EGFR (SB7) and TTF1 (SPI1) antigens were robust across a wide range of fixation times and types, as well as Iscicemia times. Conclusion: The ALK antigen is highly sensitive to fixative type, time and Iscicemia. The data indicate that the detection of ALK by IHC is impacted by fixation conditions. Strikingly, antigens detected by other lung antibodies (EGFR, TTF1) are more robust in comparison across a range of conditions. Standardized pre-analytical conditions are critical to achieve appropriate staining for ALK IHC and to mitigate the risk of false negative results. The recommendations for pre-analytical conditions for ALK are to fix at least 6 hours in 10% neutral buffered formalin.

Keywords: ALK, IHC, Fixation

POSTER SESSION 1 - P1.02: BIOLOGY/PATHOLOGY
DRIVER GENES IN NSCLC, RESISTANCE, AND OTHER – MONDAY, DECEMBER 5, 2016

P1.02-045 Discordance (FISH+, IHC-) between FISH and IHC Analysis of ALK Status in Advanced Non Small Cell Lung Cancer (NSCLC): A Unexpected Issue in 7 Cases
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Background: Discordant ALK FISH and IHC results are not uncommon. The current study aimed to assess the relationship between IHC and FISH analysis of ALK rearrangements. The current study assessed 7 cases (deleted, inverted and amplified/polysomic patterns) of ALK positive cells in FISH analysis; these complex rearranged cases were not detectable by IHC, probably due to the lack of protein expression. Considering that crizotinib inhibits the ALK protein and not specifically ALK rearrangements, it could be speculated that NSCLCs without IHC ALK expression could not be sensitive to crizotinib. The ALK FISH+/IHC negative discordant group showed a lower percentage of nuclear staining positivity for ALK rearrangement (19.3% in split signals and 21.7% in 5 deletions) as compared with 64% of gene amplification in one case and with polysomy (65.7%) observed in all cases. These preliminary data highlight the role of IHC analysis and of the percentage of the genetic pattern of ALK rearranged cells in FISH analysis to select patients for anti-ALK treatment. Further investigation is suggested about the correlation of complex mutational findings and clinical outcome.

Keywords: ALK rearrangements, advanced NSCLC, IHC/FISH discordance

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MET exon 14 skipping mutations and gene amplifications. These mutations define MET cases. Among the 14 confirmed mutations were found concomitant with MET amplification/high polysomy and protein overexpression, with discrepancies to crizotinib. Until now, patient selection has been made in view of sites, which lead to exon skipping, have been described with responsiveness to crizotinib. Our results indicate that preemptive combination therapy may be a promising strategy to prevent the emergence of MET-mediated resistance.

Keywords: dasatinib, epithelial-mesenchymal transition, third-generation EGFR-TKI, Acquired resistance

P1.02-048 MET EXON 14 SKIPPING MUTATIONS AND GENE AMPLIFICATIONS ARE NOT SIMULTANEOUS EVENTS IN NSCLC
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Background: Mutations in the MET exon 14 RNA splicing donor and acceptor sites, which lead to exon skipping, have been described with responsiveness to crizotinib. Until now, patient selection has been made in view of MET amplification, polysomy and protein overexpression, with discrepancies in positivity criteria. We investigated the prevalence of abnormal MET mutational status and the subsequent gene copy number alterations (CNAs) in NSCLC. Methods: We routinely tested 190 lung adenocarcinomas and adenosquamous carcinomas for MET exon 14 and flanking introns mutations by PCR-direct sequencing, and for MET gene CNAs by FISH (Abbott Molecular). Amplifications were defined as mean gene by mean centromere ratio ≥2.2, and high gains as mean gene ≥5.0. RT-PCR was performed to validate mutations leading to exon 14 skipping. We collected clinical-pathological data together with EGFR and KRAS mutational status, and ALK, ROS1 and RET rearrangements. Results: MET alterations were found in 34 patients (17.3%). 11 mutated cases (5.8%), eight gene amplifications (4.2%), and 15 high gains (9.1%). Six out of 11 mutations were confirmed to lead to exon 14 skipping (3.2%). Remarkably, none of these exon 14 skipped cases had concurrent MET amplification nor high gains. Although, KRAS p.G12C and EGFR 19 exon mutations were found concomitant with MET mutation in two of these cases. Among the 14 confirmed MET altered cases (6 exon 14 skipped and 8 amplified): 13 patients were male (93%), with a median age of 65.7 years (range: 40-91), nine current smokers (64%) (40 pack-years, range: 20-60), and eight diagnosed with advanced stage disease (III and IV) (57%). Correlation with cMET protein expression by IHC is ongoing, and data will be presented at the meeting. Conclusion: As no concurrent MET mutated and amplified cases were found, our data support prospective identification of both, MET exon 14 skipping mutations and gene amplifications. These mutations define a new subset of NSCLC patients that should be analyzed independently of the status of MET gene copy number.

Keywords: MET amplification, FISH, MET exon 14 skipping, MET alterations

P1.02-050 ACQUIRED RESISTANCE TO EGFR TYROSINE KINASE INHIBITORS (TKIS) IN EGFR-MUTANT LUNG ADENOCARCINOMA AMONG HISPANICS (RBIOP-CILICAP)
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Background: Patients with epidermal growth factor receptor (EGFR)-mutant lung carcinoma eventually develop acquired resistance to EGFR tyrosine kinase inhibitors (TKIs) in EGFR-MUTANT LUNG ADENOCARCINOMA AMONG HISPANICS (RBIOP-CILICAP)

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Background: Patients with epidermal growth factor receptor (EGFR)-mutant lung carcinoma eventually develop acquired resistance to EGFR tyrosine kinase inhibitors (TKIs). In 50% of these cases, a secondary EGFR mutation, T790M, underlies the acquired resistance. Other alterations include amplification of MET, P13K mutations, changes in MAPK1, Her2, AXL and even transformation to small cell lung carcinoma (SCLC). We assessed histological, clinical characteristics and survival outcomes in Hispanic patients with EGFR mutational status, and ALK translocation detected by IHC in 3.7% (12) patients. Conclusion: ELN predictive testing in primary lung adenocarcinoma patients was done in purely Caucasian Croatian population. EGFR mutation and ALK translocation rates were similar to previously published data. However, KRAS mutation rates were higher than previously published. This can be associated with high smoking rates in Croatian population.
Keywords: Activation, NGS, MET amplification, MET driver mutations.

Background: Among patients with non-small cell lung cancer (NSCLC), the frequency of MET amplification can be detected by fluorescence in-situ hybridization (FISH) is known to range from 2% to 4% in the general population. However, the presence of MET amplification increases the likelihood of resistance to EGFR-TKI treatment, and represents additional therapeutic targets. EGFR driver genes can be detected in advanced NSCLC patients. However, other driver mutations may occur simultaneously with activating EGFR mutations. The aim of this study was to compare two different commercially available probes for analysis of MET amplification, in order to optimize the amount of DNA required for FISH analysis. In order to perform this comparison, we analyzed a cohort of 27 patients with NSCLC, who had been previously tested for MET amplification and had metastatic disease. Proportion of T790M+ patients appears to be higher in the second set of samples tested with the ZytoLight SPEC ALK Dual Color Break Apart (ZYTOVISION, Ref: Z-2124-2) and was found to be underexpressed in 70% of lung tumours, ranking it in the 95th percentile of altered genes within the EGFR pathway. Immunohistochimistry (IHC) confirmed reduced protein expression in tumors, which was found to correlate with EGFR mutation and adenocarcinoma histology. In vitro, SRIPA knockout promoted migration while simultaneously inducing a dramatic decrease in cell proliferation. This phenotype is abrogated upon siRNA knockdown of SHP2. Conclusion: This phenotype is dependent upon upregulation of the CDK inhibitor p27, which hypophosphorylates RB leading to cell cycle blockade and reduced tumor growth in vivo. Importantly, increased expression of p27 resulted in mis-localization into the cytoplasm where it is known to promote an invasive phenotype. Inhibition of p27 confirmed previous findings and emphasized the importance of this pathway in lung tumorigenesis. Surprisingly, overexpression of SRIPA increased cell growth and migration, suggesting SRIPA may also possess oncogenic properties due to its regulation of multiple signaling pathways. Overexpression of SRIPA enhances the expression of SRIPA promotes migration through the inhibition of focal adhesions. This phenotype is abrogated upon siRNA knockdown of SHP2: Conclusion: SRIPA is an important player in lung tumorigenesis, capable of acting as both an oncogene and tumour suppressor due to its ability to regulate multiple signaling pathways. Effects of SHP2 and SRIPA on tumorigenesis are difficult to study in cell lines. Due to the complex nature of its signaling, future work should focus on elucidating how the timing of alterations to SRIPA affects tumorigenesis to design treatment strategy.

Keywords: non-small cell lung cancer, SRIPA, oncogene, tumour suppressor
with no nuclear overlap. Results: All cases were adenocarcinomas. Two cases showed ALK rearrangement (5.4%). Of the 34 negative cases, 27 were negative-polysomic (77.14%). One case was not assessable (2.7%) due to the impossibility of getting hybridization. Concordance between two probes was 100%. No differences were found between Papanicolaou and Diff-Quick stained smears. Conclusion: FISH-ALK in cytological stained smears gives excellent results. Both commercially available probes showed identical performance, both are equally valid. No differences were observed between Papanicolaou and Diff-Quick stained smears were observed. In our experience, stained cytological smears are the best choice for the analysis of ALK rearrangements in NSCLC patients, keeping paraffin for cases in which adequate cytological smears are not available.

Keywords: Zytolight, Vysis, ALK, cytological smears.

POSTER SESSION 1 - P1.02: BIOLOGY/PATHOLOGY DRIVER GENES IN NSCLC, RESISTANCE, AND OTHER - MONDAY, DECEMBER 5, 2016

P1.02-054 GENOMIC COMPLEXITY IN KRAS MUTANT NON-SMALL CELL LUNG CANCER (NSCLC) BY SMOKING STATUS WITH COMPARISON TO EGFR MUTANT NSCLC

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Background: KRAS is the most frequently mutated oncogene in NSCLC and lacks an effective targeted therapy. Notably, KRAS mutations occur in both never/light-smokers and smokers. However, the relationship between smoking status and a KRAS+ tumor’s genomic complexity (mutation burden, copy number changes, concurrent mutations in key oncogenic pathways) is unclear. Similarly, the relationship between genomic complexity in tumors from never/light-smokers but with a KRAS+ EGFR activating mutation is also unknown. Methods: Targeted next-generation sequencing (NGS) data at our institution from 7/13/16 was reviewed to identify KRAS+ NSCLC tumors. All patients with a 10 pack-year (py) smoking history (NS) and a subset of heavy smokers (HS) (20+ py) were identified, with clinical and genomic analysis. A comparison cohort of 48 patients with EGFR+ NSCLC was also identified. Fisher’s exact test was used to compare frequency of gene mutations. Results: 41 NS and 104 HS KRAS patients were evaluated. NS patients were more likely to be female (34/41 v 66/104, p<0.01) and diagnosed with Stage I disease (14/41 v 13/104, p<0.01). Compared to KRAS NS patients, tumors from KRAS HS patients were also genomically more complex, with increased total nucleotide variants (median+0 v 7, p<0.001) and total copy number variations (median+22.5 v 5, p<0.05). Intriguingly, in the cohort of EGFR tumors, total nucleotide variants resembled the KRAS NS cohort (median=8.5) but the total copy number variants were more similar to the KRAS HS cohort (median=25). Compared to KRAS NS tumors, KRAS HS tumors were also more likely to have: a) concurrent mutation in TP53 (43/104 v 8/41, p<0.01) and b) concurrent mutations/2 copy deletions in s1 tumor suppressor (TS) tumor (median=17, 35/104 v 17/41, p=0.004). While the total number of nucleotide variants in the EGFR cohort was most similar to the KRAS NS cohort, TS distribution in these EGFR tumors was closer to the KRAS HS cohort (TP53 variants in 31/48 and multiple TS variants in 14/48). Finally, median OS for KRAS HS patients with Stage IV disease was 9.7m v 28.7m in KRAS NS patients (HR=0.56). Conclusion: The genomic landscape of KRAS+ NSCLC from HS patients is distinct from NS patients and includes increased total mutations and frequency of TS loss. EGFR mutant tumors show some similarities with KRAS tumors from both NS and HS patients. Overall, NS KRAS+ tumors may be a genetically distinct cohort within the broader context of KRAS+ NSCLC.

Keywords: KRAS, Genomics, NSCLC

POSTER SESSION 1 - P1.02: BIOLOGY/PATHOLOGY DRIVER GENES IN NSCLC, RESISTANCE, AND OTHER - MONDAY, DECEMBER 5, 2016

P1.02-055 TUMOR HETEROGENEITY IN LESION SPECIFIC RESPONSE CREATES ROS1 FUSION MEDIATING RESISTANCE TO GEFITINIB IN EGFR 19 DELETION LUNG ADENOCARCINOMA

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Background: Non-small lung cancer (NSCLC) is one of the leading cause of cancer related death worldwide. In recent years molecular characterisation of NSCLC has led to the identification of several driver events including EGFR constitutive activation, ALK-rearrangement and ROS1 fusion. Whilst there are several mechanisms of EGFR-mutation stated in the literature, how genomic heterogeneity related with acquired EGFR resistance to second targeted agent affects response to subsequent therapy has not been noted. Methods: We studied EGFR-TKI, gefitinib, in an EGFR 19 deleted lung adenocarcinoma patient to assess whether tissue and liquid biopsy could be integrated with radiologic imagings to demonstrate the impact of individual actionable driver mutation on lesion specific response. Results: A 60-year old female, with no previous or family history of malignancy initially presented with EGFR 19 deletion mutation, ROS1 fusion negative and ALK rearrangement negative stage IV, T2aN3M1a lung adenocarcinoma detected in primary lung cancer tissue at the first diagnosis. Biopsy of this patient’s metastatic right cervical lymph node following prolonged response to gefitinib led to the loss of detection of EGFR mutation, and the novel mechanism of acquired resistance with EZR-ROS1 fusion where crizotinib was demonstrated to have good efficacy in all lesions, especially the enlarged lymphadenopathy, and also including diminishing efficacy on metastatic brain lesions. In circulating tumor DNA (ctDNA), mutant EGFR levels disappeared following gefitinib treatment, and a recognized EZR-ROS1 fusion was meanwhile identified before crizotinib therapy. Conclusion: This case displays tumor heterogeneity in action, where targeted therapy selects against primary drivers, allowing for the establishment of sub-colonies with new drivers within the specific lesion. Parallel analysis of tumor biopsies when disease progressed and ctDNA monitoring showed that lesion specific radiographic responses to subsequent targeted therapies could be driven by district resistant mechanism in the separate tumor lesions within the same patient. This demonstrates that the importance of molecular heterogeneity surveillance ensuing from acquired
Background: Advanced NSCLC patients whose tumors harbor ALK fusions benefit from first line treatment with ALK inhibitors (ALKi). However, insufficient tissue for testing (QNS) occurs ~25% of the time. Patients treated with ALK inhibitors ultimately progress. Historically, identification of the resistance mechanism(s) required repeat tumor biopsy. Circulating tumor DNA (ctDNA) may provide a non-invasive way to identify ALK fusions and actionable resistance mechanisms without a repeat biopsy. Methods: The Guardant360 (G360) ctDNA assay was used to profile tumor ctDNA in 104 NSCLC patients with tissue available at the local institution. ctDNA was extracted from 4 ml of blood drawn into the Guardant360 blood tube and amplified via Ion Torrent (Ionpike) sequencing. The ctDNA results were compared with historical testing for ALK fusions and actionable mutations when available. Results: Of the 104 patients, 70 (67%) had QNS. Of those with QNS only (n=70), 33 (47%) patients had ALK positive ctDNA and no fusion detected; historical tissue testing was +. Conversely, in cohort 1, 10 (33%) were tissue CTNNB1 or STRN or ALK negative while 4 (13%) were tissue TP53 or 3 (2 patients) BRAF +. No documented or putative resistance mechanisms were identified in cohort 1, although TP53 mutations were identified in 43%. Among 18 patients progressing on an ALK inhibitor, 7 (39%) contained 1 (4 patients), 2 (1 patient) or 3 (2 patients) ALK resistance point mutations L1196M; 3 (1 patient) or 2 (1 patient) had no history of targeted therapy (new diagnosis or prior genotyping), “cohort 2”. In 6 samples, the patients’ clinical status was unknown. Three additional cases had ALK resistance point mutations L1196M; 3 (1 patient) or 2 (1 patient) were tissue ALK+ and 16 (54%) had unknown tissue status. As expected, no documented or putative resistance mechanisms were identified in cohort 1, although TP53 mutations were identified in 43%. Among 18 patients progressing on an ALK inhibitor, 7 (39%) contained 1 (4 patients), 2 (1 patient) or 3 (2 patients) ALK resistance point mutations L1196M; 3 (1 patient) or 2 (1 patient) had no history of targeted therapy (new diagnosis or prior genotyping), “cohort 2”.

Conclusion: These results add to the growing body of literature demonstrating that comprehensive ctDNA assays can provide a non-invasive means of detecting targetable alterations in the first line treatment with ALK inhibitors. However, increased sensitivity and specificity will help to maximize sensitivity and specificity.

Keywords: EGFR, mutation, amplification, outcome
P1.02-060 EGF MEDIATES ACTIVATION OF RET IN LUNG ADENOCARCINOMA WITH NEUROENDOCRINE DIFFERENTIATION CHARACTERIZED BY ASCL1 EXPRESSION

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Background: Achaete-scute homolog 1 (ASCL1) is a neuroendocrine transcription factor expressed in 10-20% of lung adenocarcinomas (AD) with neuroendocrine (NE) differentiation. Previously, we demonstrated that ASCL1 functions as an upstream regulator of the RET oncogene in AD with high ASCL1 expression (A-AD). In this study, we examined the potential role of wild type RET in influencing the oncogenic properties of A-AD. We also screened for drugs that could selectively target RET signaling and examined the role of the two RET isoform separately. Methods: The association of the mRNA expression for the long (RET51) and short (RET9) RET isoforms with overall survival (OS) were assessed in a case-control study of stage-1 A AD patients surgically resected at the Mayo Clinic (1994-2007). Cases and controls were defined as patients who survived <3.5 years after surgery (n=29) and ≥ 5 years after surgery (n=38), respectively. mRNA was isolated from FFPE tissue and analyzed by a Nanostring assay. Associations of each isoform mRNA with the OS was determined by the area under the receiver operating characteristic curves (AUC). For drug screening, HCC1833 lung AD cells with endogenously high expression of ASCL1 were stably transfected with either empty vector or an ASCL1-shRNA. Differential sensitivities of tyrosine kinase inhibitors (TKIs) in the pair of syngeneic cell lines were measured by Cell-Titer Glo (Promega). Interactions between EGFR and RET was examined by co-immunoprecipitation. Results: Expression of RET51 mRNA was associated with poor OS (p=0.005, AUC 0.71). We detected modestly increased sensitivity to sunitinib and vandetanib in A AD compared with A-AD cells. However, the EGFR inhibitors gefitinib and the dual EGFR and HER2 inhibitor lapatinib resulted in ≥10 fold higher cytotoxicity in A AD cells than in A-AD cells. Subsequent experiments demonstrated that EGFR stimulation of EGF mediates the phosphorylation of RET in multiple A-AD cells. RET and EGFR were found to interact only in presence of EGF and predominantly through the long RET isoform (RET51). Conclusion: Herein we demonstrate that wild type EGFR predominantly interacts with the long isoform of RET (RET51) in A AD cells. EGFR stimulation of RET51 in A AD cells appears to be more sensitivity to EGFR inhibitors. In summary, our results suggest that A AD patients may benefit from treatment with EGFR inhibitors even in the absence of an EGFR mutation.

Keywords: ASCL1, neuroendocrine, RET, EGF

P1.02-062 CONSENSUS OF GENE EXPRESSION PHENOTYPES AND PROGNOSTIC RISK PREDICTORS IN PRIMARY LUNG ADENOCARCINOMA

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Background: Transcriptional profiling of lung adenocarcinomas has identified numerous gene expression phenotype (GEP) and risk prediction (RP) signatures associated with patient outcome. However, classification agreement between signatures, underlying transcriptional programs, and independent signature validation are less studied. Methods: Published transcriptional profiles from 17 cohorts comprising 2395 lung adenocarcinomas with available patient outcome data were collected from authors’ websites or public repositories as described in the original studies. Tumors were classified according to 18 different GEPs or RPs derived from microarray analysis of lung adenocarcinoma or NSCLC cohorts, using reported original classification schemes or consensus clustering of gene signatures on a per cohort basis. To independently assess the accuracy of these classification methods by the lung cancer derived signatures and classification by expression of proliferation-related genes only, a 155-gene breast cancer signature was used to classify all tumors as low-proliferative (average expression of the 155-genes median) or high-proliferative. Tumors were also scored according to five reported expression metagenes in lung cancer representing different biological processes; proliferation, immune response, basal / squamous, stroma / extracellular matrix (ECM), and expression of Napsin A / surfactants on a per cohort basis to contrast subtype classifications with biological functions. Results: 16 out of 18 signatures were associated with patient survival in the total cohort and in multiple individual cohorts. For significant signatures, total cohort hazard ratios were −2 in univariate analyses (mean=1.95, range=1.4-2.6). Signatures derived in adenocarcinoma generally displayed better classification agreement than signatures derived in mixed NSCLC cohorts. Strong classification agreement between signatures was observed especially for predicted low-proliferative patients by adenocarcinoma-derived signatures, despite a generally low gene overlap. Expression of proliferation-related genes correlated strongly with GEP subtype classifications and RP scores, driving the gene signature association with prognosis. A three-group consensus definition of samples across 10 GEP classifiers demonstrated classification of samples with specific smoking patterns, gender, and EGFR/ KRAS mutations, while survival differences were only significant when patients were divided into low- or high-risk resembling a terminal respiratory (TRU) like and non-TRU division, respectively. Conclusion: By providing this consensus classification of GEPs and RPs in lung adenocarcinoma we have connected molecular phenotypes, risk predictions, patient outcome and underlying transcriptional programs of the different classifier types. Our results provide a general insight into the nature and agreement of GEP and RP signatures in the disease, and their prognostic value.
Background: Targeting the MAPK pathway by MEK inhibition results in limited activity in patients with KRAS-mutant non-small cell lung cancer (NSCLC). The lack of effectiveness may be associated with activation of other effectors including STAT3, as well as MEK inhibition reliance from negative feedback loops. Indeed, in KRAS-mutant colorectal cancer, MEK inhibition decreases the activity of the metalloprotease ADAM17, which normally inhibits MET signaling and STAT3 activation by promoting shedding of MET endogenous antagonist, soluble “decoy” MET. Herein, we explore the MET-dependent activation of STAT3 as a mediator of resistance to MEK inhibitors, and whether MET or STAT3 inhibitors can synergistically increase MEK-inhibitor induced growth inhibition in KRAS-mutant NSCLC cells in vitro. Methods: Cell viability was assessed by MTT (thiazolyl blue) assay after treatment with the MEK inhibitor selumetinib, the small-molecule dual inhibitor of the MET and ALK receptor tyrosine kinases, crizotinib, and evodiamine, an alkaloid isolated from the dried, unripe Evodia rutaecarpa (Juss.) Benth fruit, that exerts an antitumor effect by inhibiting STAT3. RNA was isolated from four KRAS cell lines and the STAT3 and MET mRNA expression analysis was performed by TaqMan based qRT-PCR. Western blotting was used to assess the effect of selumetinib on ERK, AKT and STAT3 phosphorylation. Results: We first evaluated the efficacy of the MET inhibitor selumetinib in our KRAS-mutant NSCLC cell line panel using an MTT cell proliferation assay. H460 cells were relatively insensitive to selumetinib. Following 48-hour treatment with selumetinib, ERK1/2 and AKT phosphorylation were suppressed but a rebound activation of STAT3 occurred in H460 cells. We next investigated whether MET expression was related to the feedback activation of STAT3 signaling following MEK inhibitor treatment. We compared gene expression profiles of the H460 cell line before and after treatment with selumetinib. Interestingly, we found significant upregulation of MET and STAT3 mRNA expression after seven days of selumetinib treatment. To further interrogate the relationship between MEK inhibition and MET-mediated STAT3 reactivation, H460 cells were treated with the combination of selumetinib and crizotinib or selumetinib and evodiamine. A 72-hour exposure to both combinations resulted in a clear cell synergism, as measured by the combination index (CI) analysis, with a CI of 0.79 and 0.78 respectively. Conclusion: Collectively our results showed that the feedback STAT3 activation induced by MET, mitigates the effect of MEK inhibition, and provides rationale for further assessment of combined MEK and MET or STAT3 inhibition in KRAS-mutant NSCLC.

Keywords: lung cancer, KRAS, STAT3, MEK inhibitors
examined by Western blot analysis, cell titre blue and BrdU assay respectively. Results: All three PIM isoforms were detected in the lung cancer cell lines tested. Similarly, all three PIM isoforms were expressed across the 31 NSCLC patient tumour and match normal adjacent tissue samples. To investigate this further PIM1 staining of FFPE tumour and match normal tissue from this cohort is currently underway. In two lung cancer cell lines, H1975 and H1838, IBL-301 was found to have a dose dependent effect on proliferation/viability with IC50 values in the nanomolar range. Additionally, western blot analyses have indicated that novel drugs can suppress the phosphorylation of key players in cell signalling pathways linked to tumorigenesis including pAkt, p4E-BP1 and pellF4. Conclusion: This is the first study to investigate the expression of all 3 isoforms of PIM in lung cancer specifically. All 3 isoforms were abundantly expressed across cells lines and patient tumour samples. Observed PIM expression in the immune cells of normal adjacent tissue may indicate a role in inflammation. This finding coupled with the promising in vitro data demonstrate the therapeutic potential of targeting PIM in NSCLC.

Keywords: Pim kinase, biomarker, therapeutic target, NSCLC

P1.02-066 GENOMIC PROFILING IN THE DIFFERENTIAL DIAGNOSTICS OF PULMONARY TUMOURS: A CASE SERIES
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Background: Histopathological diagnosis is important for prognostication and choice of treatment in patients with cancer in the lung. Lung metastases are common and need to be distinguished from primary lung cancer. Furthermore, cases with synchronous or metachronous primary lung cancers (although infrequent) are often handled differently than cases with lung cancer with intrapulmonary metastasis or relapse, respectively. In some cases, morphology and immunohistochemical (IHC) staining is not sufficient for certain diagnosis. Methods: Five cases were selected where molecular genetic analysis in form of pyrosequencing or targeted next-generation sequencing (NGS) was of value, not only for treatment prediction, but for certain diagnosis of tumours in the lung. Results: Two of the included cases were rare metastases to the lung – rectal cancer with IHC profile consistent with primary lung cancer and malignant myoepithelium of the breast, respectively – where molecular genetic analysis was of aid for proving the relationship with the primary tumour. The other three cases had multiple lung adenocarcinomas with similar morphology where molecular genetic analysis was of aid to distinguish between an intrapulmonary metastasis and a synchronous primary tumour. Conclusion: Comparison of molecular genetic profile may be an important tool for determination of relationship between tumours, at least in selected cases, and should always be considered in unclear cases. Further studies on concordance and discordance of molecular genetic profiles between spatially or temporally different tumours with common origin may be helpful for improved diagnostics of pulmonary tumours.

Keywords: next-generation sequencing, pyrosequencing, histopathology, metastasis

P1.02-067 REPEATED BIOPSY FOR IMMUNOHISTOCHEMICAL AND MUTATIONAL ANALYSIS OF NON SMALL CELL LUNG CANCER: FEASIBILITY AND SAFETY
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Background: Repeated biopsy in lung cancer may be necessary at diagnosis or after cancer progression on initial therapy to properly target treatments. The objective of this study is to evaluate the feasibility and safety of repeated biopsy for immunohistochemical and/or mutational analysis in patients with non small cell lung cancer. Methods: We have retrospectively analyzed repeated biopsies performed in patients with advanced non small cell lung cancer during the last 4 years. The technical success rates for the repeated biopsy and the adequacy rates of specimens were evaluated. Biopsy-related complications were recorded. Clinical details were collected, specially focusing in EGFR mutation data. Results: 10 repeated biopsies were performed in 74 patients (34 women, 40 men, mean age 63 [36-84]). The histology was: 74% adenocarcinoma, 12% squamous cell carcinoma, 1% NOS, 3% other. The mean number of repeated biopsies per patient was 1 (1-4). The main reasons for repeated biopsy were immunohistochemical +/- mutational analysis (34/110, 31%), mutational analysis (16/110, 34.6%), and EGFR at progression (28/110, 24.4%). The technical success rate for biopsy was 98/110 (89.1%), and postprocedural complications occurred in 3/110 cases: 2 pneumothorax and 1 wound infection. Biopsy specimens came mostly from primary tumor (56/110, 51%), lymph nodes (26/110, 23.6%) and pleura (9/110, 8.2%). The most used technique was bronchoscopy +/- BUS (45/110, 40%), followed by percutaneous transthoracic lung biopsy (28/110, 26%) and thoracoscopy and/or mediastinoscopy (19/110, 17%). Results from repeated biopsy were used to select the next line of treatment in 86/110 procedures (78%), and 40/86 of them (46.3%) allowed to include the patient in a clinical trial. 28 repeated biopsies were performed in 21 EGFR mutant lung cancer patients with acquired resistance at disease progression, T790M was detected in 13/28 (46%) of samples, corresponding to 10/21 (47.6%) EGFR mutant lung cancer patients. Conclusion: Our data demonstrate that repeated biopsy in non small cell lung cancer is safe and clinically feasible. Findings from repeated biopsy were used to direct subsequent treatment in 78% of patients.

Keywords: repeated biopsy, Acquired resistance in EGFR mutant lung cancer

P1.02-068 THE IMPACT OF TP53 OVEREXPRESSION ON EMT AND THE PROGNOSIS IN LUNG ADENOCARCINOMA HARBOURING DRIVER MUTATIONS
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Background: Epithelial-mesenchymal transition (EMT) and p53 mutations are known to be pivotal for driving metastasis and recurrence in lung cancer, but the nature of these factors is not completely understood. Some papers have previously described the relationship between EMT and TP53 in other carcinomas, however there have been few reports about the impact of TP53 on EMT and prognosis in lung adenocarcinoma harboring driver mutations such as EGFR or K-Ras. Methods: A total of 282 EGFR adenocarcinoma specimens were collected from patients who had undergone surgery in our institute from January 2001 to December 2007. Both EMT markers (E-cadherin, vimentin) and TP53 were analyzed through immunostaining of tumor specimens. The association between EMT and TP53 as well as the patients’ clinical information was integrated and statistically analyzed. EGFR and K-ras mutation were determined by single stranded conformational polymorphism and direct sequencing. Correlations were compared using Pearson’s chi-square test and overall survival were compared using the log-rank test. Results: Both mesenchymal type (E-cadherin negative, vimentin positive) and TP53 overexpression were significantly correlated with poor prognosis (P=0.0001, P=0.0019). A positive correlation was found between EMT activation level and TP53 overexpression (P=0.017). TP53 overexpression was significantly correlated with poor prognosis in the subgroup of lung adenocarcinoma with driver mutation (EGFR or K-ras) (P=0.011, P=0.026), whereas there was no significant correlation between TP53 overexpression and the prognosis in adenocarcinoma without driver mutations (P=0.359). Conclusion: TP53 overexpression is supposed to be the key factor that affects EMT and the prognosis, and also might be an additional therapeutic target for lung adenocarcinoma with driver mutations.

Keywords: Driver mutation, TP53, epithelial-mesenchymal transition, lung adenocarcinoma

P1.02-069 GENOMIC ALTERATIONS AND SURVIVAL IN YOUNG PATIENTS UNDER 40 YEARS WITH COMPLETELY RESECTED NON-Small Cell Lung Cancer
MONDAY, DECEMBER 5, 2016

POSTER SESSION 1: P1.02: BIOLOGY/PATHOLOGY OTHER MUTATIONS IN THORACIC MALIGNANCIES – MONDAY, DECEMBER 5, 2016

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P1.02-070 GENE SPECTRUM AND SURVIVAL ANALYSES OF PATHOLOGIC SUBTYPES IN RESECTED LUNG SQCC CELL CARCINOMA

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Background: Based upon the 2015 Lung Cancer Pathologic Classification, squamous cell carcinoma of lung (SQCC) has been classified as three types of keratinized, non-keratinized and basaoid squamous cell carcinoma (BSCC). The spectrum of common driver genes and clinical prognosis were examined for different subtypes in SQCC in present study. Methods: From 2009 to 2013, a total of 201 patients with completely resected stages I-IIIA SQCC were recruited. Reverse transcription-polymerase chain reaction (RT-PCR) was utilized for detecting the mutations of EGFR, KRAS, NRRAS, PIK3CA, BRAF, DDR2, HER2 and the fusion genes of ALK, ROS1 and RET. Survival curves were plotted with Kaplan-Meier method. Cox proportional hazard model was used for multivariate analysis. Results: The pathological types were BSCC (n=16), non-keratinizing (n=83) and keratinizing (n=102). The frequency of gene abnormality was 18.4%. The most common driver genes in decreasing frequency were PIK3CA mutation (n=16), EGFR mutation (n=8), DDR2 mutation (n=8), KRAS mutation (n=3), HER2 mutation (n=2), ALK rearrangement (n=1) and ROS1 rearrangement (n=1). No mutations of NRAS, BRAF or RET were observed. The frequency of gene abnormality was greater in keratinized (19.6%) followed by non-keratinized (19.2%) and BSCC types (6.3%). Targeted therapy was offered for 35 patients, including 32 on EGFR-TKIs (EGFR mutation, n=5; EGFR wild-type, n=27), ALK-positive on crizotinib (n=1) and HER2 mutation on afatinib (n=1). The median progression-free survival (PFS) of EGFR-TKIs were 6.0 and 1.87 months in EGFR mutant and wild types respectively (P=0.004). And the PFS for those two with crizotinib and afatinib treatment were 8.0 and 3.5 months respectively. The SQCC patients of BSCC subtype had significantly worse overall survival than those with non-BSCC subtypes (29.0 vs.47.0 months, P=0.01). Conclusion: The subtypes of SQCC were associated with varying frequency of gene abnormality. BSCC had a lower frequency of common driver gene abnormality and worse survival.

Keywords: Pulmonary squamous cell carcinoma, Basaoid squamous cell carcinoma, gene abnormality, survival

P1.02-070 COMPREHENSIVE GENOMIC ALTERATIONS IDENTIFIED BY NEXT-GENERATION SEQUENCING OF LUNG ADENOCARCINOMA IN JAPANESE POPULATION

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Background: Therapeutic approaches to lung cancer have shifted toward an emphasis on molecularly targeted therapy in genotypic subsets of patients (pts). Recent advances in next-generation sequencing (NGS) technologies have improved the ability to detect potentially targetable mutations. In this study, we aimed to analyze the genomic alterations of lung adenocarcinoma. Methods: A retrospective analysis of genomic data obtained from 99 archived formalin-fixed, paraffin-embedded samples from Japanese pts with lung adenocarcinoma were analyzed by NGS panel of 415 genes. Mutations and frequency of variants present in key oncogenic drivers for each pts were quantified. Fisher’s exact and t-tests were used to identify associations between genomic alterations and clinical characteristics. Results: Sex: male 66 pts, female 33 pts. Smoking status: pack-year (PY) <30 (light smoker) 61 pts, PY≥30 (heavy smoker) 30 (10.62% (155/1659) for 58SBR mutation, respectively. Minor genetic alterations, except major mutation, in EGFR were detected in 82.8% (48/58) cases, and the mean number was 2.3 (0-11). These results suggest the clinical applicability of this method. Conclusion: We could demonstrate good concordance rate of this method. Other Mutations in Thoracic Malignancies – Monday, December 5, 2016

P1.02-071 DETECTION OF MULTIPLE LOW-FREQUENCY MUTATIONS BY MOLECULAR-BARCODE SEQUENCING

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Background: Young patients diagnosed as non-small cell lung cancer (NSCLC) is rare. Little is known for its genomic alterations and survival. This study retrospectively evaluated the genomic alterations, treatment and prognosis with NSCLC in our institution between January 2009 and July 2014. Methods: All patients were examined for EGFR, KRAS, NRAS, PIK3CA, BRAF, HER2 mutations and ALK, ROS1, RET fusion genes based on reverse transcription PCR. The Kaplan-Meier method was used to estimate survival and comparison using the log-rank test. Results: Totally, 54 were with age under 40 years old among 640 patients. Among the 640 patients, three hundred and fifty eight were with identified genomic alterations with frequency of 55.9%. The frequencies of genomic alterations in younger and older were 68.5% and 54.8%, respectively (P=0.05). The frequencies difference between younger and older existed in fusions genes (22.2% vs.4.1%, P<0.001), but not mutations genes (46.3% vs.45.6%, P=0.92). There was a trend of shorter recurrence free survival in younger than older (35.2 vs.43.8 months, P=0.050), while no survival difference was found between younger and older (50.2 vs 51.4 months, P=0.112). Conclusion: We concluded that younger age of NSCLC is associated with a trend of increased of harboring targeted genes and mainly with difference of fusion genes. An inferior overall survival existed in younger than older.

Keywords: non-small cell lung cancer, age, survival, genomic alterations
TP53 (40%), CDKN2B (32%), RB1 (21%), and CDKN1B (19%). Representative genomic alterations with a FDA approved targeted therapy such as EGFR mutation (exon 19 deletion and exon 21 L858R), ALK fusion, ROS1 fusion, RET fusion, BRAF (V600E) mutation and, MET amplification were detected in 56 pts (R-GAs group) and the others were 43 pts (O-GAs group). In the O-GAs group, 39 pts had genetic alteration with targeted agent available on or off a clinical trial. As for smoking habit, R-GAs group were significantly associated with light smoker than O-GAs group (p<0.01). In R-GAs group, the median number of mutation burden and actionable mutation were 13 (range 5-20) and 4 (range 1-10), respectively. O-GAs group were significantly greater mutation burden and actionable mutation than R-GAs group (16.2 ± 8.8 vs. 12.3 ± 4.3, p<0.01; 6.5 ± 5.0 vs. 4.5 ± 2.2, p = 0.02, respectively). Of the 43 EGFR cases, 38 (88%) pts had further genetic alteration with targeted agent available on or off a clinical trial excluding EGFR TKI. Conclusion: With help of NGS, we found most pts might be treated by targeted therapies. Further study may emerge whether concurrent mutations, mutation burden and the number of actionable mutations are associated with survival outcome in lung adenocarcinoma.

Keywords: next-generation sequencer, lung adenocarcinoma, genomic alteration

P1.02-073 CHARACTERIZING THE GENOMES OF LUNG ADENOCARCINOMAS FROM NEVER SMOKERS REVEALS SHPRH AS A NOVEL CANDIDATE TUMOUR SUPPRESSOR GENE

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Background: Approximately 15 to 25% of lung adenocarcinomas (LAC) arise in never smokers. They develop through mechanisms distinct from those that affect smokers and are associated with unique histological and molecular characteristics. A significant fraction of LACs in never smokers do not have mutations in known oncogenic driver genes such as EGFR/ALK/KRAS. Furthermore, mutations in oncogenic driver genes appear to be insufficient for tumorigenesis, suggesting that additional alterations are required.

Methods: To address these issues, we used whole-exome sequencing to comprehensively study 15 LACs from never smokers - seven "triple negative" tumors (with normal EGFR/ALK/KRAS) and eight EGFR-mutant tumors - with the goal of identifying novel mutant genes in these subsets. To identify mutated genes that confer a selective advantage a multistep approach was used to filter variants based on gene expression level, background mutation rate and gene size. Targeted sequencing of 180 genes in the original 15 and indicated their prevalence in LAC. Sequence data was integrated with copy number and gene expression levels to determine mechanisms, and consequences, of gene disruption. Animal and cell models were used to functionally validate identified genes of interest and explore their role in LAC biology. Results: 32 unique genes demonstrated significant evidence of conferring a selective advantage including known oncogenes (EGFR/ERBB2/ MET) and tumor suppressor genes (p53/RB1/ATM). In addition, RNA-seq revealed fusion oncogenes (FUS, or ROS1) in one tumor sample. The variations in MET consisted of truncating and splice-site mutations that we are currently investigating in transgenic mouse models. Pathway analysis indicated frequent mutation in genes implicated in PI3-kinase signaling, RNA splicing and histone modification. Importantly, we identified the hemizygous and homozygous loss of multiple genes from chromosome arm 6q - a genomic locus associated with familial lung cancer susceptibility - including a novel candidate tumor suppressor gene, SHPRH, based on its high frequency of biallelic disruption. SHPRH is an evolutionarily conserved E3-ligase that mediates ubiquitination related to DNA repair. We found that SHPRH silencing increased transformation of normal lung cells, increased DNA damage and induced cell cycle changes while SHPRH inhibition sensitized LAC cells to topoisomerase II and PARP inhibitors. Conclusion: SHPRH inactivation may induce genetic alterations that cooperate with mutations in driver oncogenes and tumor suppressors. Together, this work will expand our understanding of LAC initiation and progression in never smokers and may offer new biomarkers for response to therapy.

Keywords: Genomics, NSCLC, mouse models, oncogene signaling

P1.02-074 THE GENE EXPRESSION SIGNATURES OF PULMONARY ADENOCARCINOMA WITH MICROPAPILLARY FEATURES

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Background: Invasive lung adenocarcinomas have been classified into 5 subtypes by the new WHO classification, of which micropapillary–predominant subtype is known to have a poor prognosis. However, we previously reported that lung adenocarcinomas harboring a micropapillary component (MPC) of more than 5% showed poorer disease-free survival and overall survival in comparison to the other subtypes (JTCVS 152: 64-72; 2016), despite the MPC not being predominant. Specific biomarkers for the MPC are yet to be developed for the initial diagnosis of adenocarcinoma with an MPC. Methods: Total RNA was extracted from snap frozen archived lung adenocarcinoma samples that had been obtained by radical thoracotomy. The diagnosis of each subtype was made by independent pathologists using formalin-fixed paraffin-embedded samples. Frozen sections were made using the archived frozen sample; RNA was isolated after the confirmation of the diagnosis of each sample. RNA-sequencing was conducted using 22 adenocarcinomas and 3 normal lung tissue samples. The 22 adenocarcinomas included micropapillary (n=6), papillary (n=5), lepidic (n=5), acinar (n=3) and solid (n=3) subtypes. The reads per kilo base of exon per million mapped reads data derived from RNA-sequencing were calculated to analyze the gene expression profiles of the MPCs. The expression levels of the genes were validated by a real-time PCR. Results: A hierarchical clustering analysis revealed a cluster of tumor samples with MPCs. Two hundred four genes were differentially expressed in adenocarcinomas that contain an MPC. Gene-ontology analysis showed the enrichment of signal-related genes, with 50 significantly upregulated genes, including BAMBI, CXCL14 and VSIG1. Conclusion: The results of a gene expression analysis using next generation sequencing revealed the specific gene expression profile of adenocarcinomas that contain an MPC, and several genes might be candidate diagnostic biomarkers for the subtype. In addition, these genes may play an important role in the unique characteristics of adenocarcinomas that contain an MPC.

Keywords: RNA-sequencing, Micropapillary component, Biomarker, Gene Expression

P1.02-075 ANALYSIS OF DRIVER GENES ALTERATION AND CLINICOPATHOLOGICAL FEATURES IN PULMONARY MARKER-NULL LARGE CELL CARCINOMA

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Background: Pulmonary large cell carcinoma (LCC) was an undifferentiated and marker-null small cell lung cancer (NSCLC) according to 2015 WHO classification criteria. However, there are few studies presented molecular analysis and clinical features of this subtype. The aim of this study is to investigate profile of driver genes and clinicopathological features of marker-null LCC. Methods: From January 2008 to February 2015, 327 cases of surgically resected primary large cell carcinoma diagnosed by H&E staining were enrolled from Shanghai pulmonary hospital affiliated to Tongji university (Lymphoepithelioma-like carcinoma and large cell neuroendocrine carcinoma were excluded with typical morphologic features). Large cell carcinoma was reclassified with a panel of immunophenotypic markers (adenocarcinoma [AD]--specific, thyroid transcription factor-1, napsin A and anti-diastase PAS staining; squamous cell carcinoma [SQCC]--specific, cytokeratin5/6, and p40; epithelial mesenchymal transition (EMT), cytokeratin, vimentin and ZEB1; neuroendocrine differentiation, synaptophysin and CD56). Molecular analysis (EGFR, KRAS, BRAF, ROS1, ALK and PIK3CA) and immunomarker PD-L1 of the diagnosis of each sample. RNA-sequencing was conducted using 22 adenocarcinomas and 3 normal lung tissue samples. The 22 adenocarcinomas included micropapillary (n=6), papillary (n=5), lepidic (n=5), acinar (n=3) and solid (n=3) subtypes. The reads per kilo base of exon per million mapped reads data derived from RNA-sequencing were calculated to analyze the gene expression profiles of the MPCs. The expression levels of the genes were validated by a real-time PCR. Results: A hierarchical clustering analysis revealed a cluster of tumor samples with MPCs. Two hundred four genes were differentially expressed in adenocarcinomas that contain an MPC. Gene-ontology analysis showed the enrichment of signal-related genes, with 50 significantly upregulated genes, including BAMBI, CXCL14 and VSIG1. Conclusion: The results of a gene expression analysis using next generation sequencing revealed the specific gene expression profile of adenocarcinomas that contain an MPC, and several genes might be candidate diagnostic biomarkers for the subtype. In addition, these genes may play an important role in the unique characteristics of adenocarcinomas that contain an MPC.

Keywords: RNA-sequencing, Micropapillary component, Biomarker, Gene Expression
Syn expression. 26 (26/327, 8.0%) were redefined as sarcomatoid carcinoma expressed cytokeratin, vimentin and ZEB1. 136 (136/327, 41.6%) cases of marker-null SCC were diagnosed for lack of specific markers expression. 30 (30/136, 22.3%) cases of marker-null SCC showed PD-L1 however, the clinicopathological characteristics indicated that HCC patients were older and more likely to be male nonsmokers. Conclusion: Large cell carcinoma was differentially diagnosed by combining with undifferentiated NSCLC morphology and marker-null features. Driver genes mutation testing may significantly impact on the choice of targeted therapy.

Keywords: large cell carcinoma, molecular analysis, differential diagnosis, clinical features
Background: The youthful lung cancer may constitute an entity with distinct clinicopathologic characteristics. The serine/threonine kinase LKB1, also known as Serine/Threonine Kinase 11-STK11, is a known tumor suppressor gene involved in cellular responses such as energy metabolism, cell polarity and cell growth, but the role of LKB1 pathway in lung adenocarcinoma (ADC) is barely studied, especially in young patients. Methods: Fifty lung ADC patients were retrospectively analysed. After RNA purification from formalin fixed and paraffin embedded tumor tissues, we analysed the mRNA expression levels of genes involved in cell survival pathways, such as cyclin D1 (CCND1), beta catenin (CCNB1), lysyl oxidase (LOX), yes-associated protein-1 (YAP-1), and survivin, with NanoString technology, a new tool for a more accurate expression profiling. KRAS mutations were investigated by pyrosequencing analysis. Clinicopathologic characteristics and survival analysis were available for all patients. Results: Patients under 50 years old (including 50) were defined as the younger group and patients above 50 years old were defined as the older group. Among all the clinicopathologic characteristics, in the younger group there were more women, less solid and more acinar adenocarcinoma prevalent pattern in comparison to the older group. Younger and older groups showed similar survival rates, as well as KRAS mutations frequencies. Also, in the comparison between the gene expression level of the analyzed genes and the two different age subgroups, no statistical difference was found. We then focused on the LKB1 pathway in all series, independently from the age stratification, founding LKB1 low expression associated with low cyclin D1 (CCND1) (p=0.0001), beta catenin (CCNB1) (p=0.0001), and YAP1 (p=0.0024) levels, suggesting a target regulation by LKB1 in order to identify potential target for lung cancer therapy. Results: All cases were successfully tested and somatic alterations were found in all ADC and three AAH/AIS lesions. None of the samples had an ALK rearrangement. Patient 3, with two ADC, had different profiles between all three lesions tested. In Patient 6, the ADC had an activating EGFR p.L858R mutation and the synchronous AJH/AIS lesion showed a KRAS p.G12D mutation.

Keywords: lung adenocarcinoma, LKB1 pathway, expression analysis

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Background: Atypical adenomatous hyperplasia (AAH) is considered the precursor lesion of adenocarcinoma (ADC), and adenocarcinoma in-situ (AIS) the early invasive phase of invasive ADC. Finding incidental synchronous AIS/ AAH within lung resection specimens of ADC is an opportunity to evaluate and compare the genomic profiles of the lesions. Different mutation profiles would suggest a field effect with the formation of an early second primary. Identical mutations might suggest a closer relationship with the primary tumor such as an early intrapulmonary metastasis from spread through air spaces. In this study we evaluate the genomic profiles of synchronous AIS/AAH lesions and separate primary ADC in the same lobes of resection specimens. Methods: We tested the 13 lesions from six patients identified between August 2015 and June 2016 by targeted next generation sequencing (NGS) using the 50 gene Ampliseq Cancer Hotspot Panel v2 and FISH for ALK rearrangements. All of our patients had a single radiographically evident ADC and one patient had a second smaller lesion which was proven ADC at resection. All six patients had at least one additional incidental focus of AIS/AAH, not detected radiographically. Our patients ranged in age from 51-67. Five patients were female (83%) and all were current or former smokers.

Results: All cases were successfully tested and somatic alterations were found in all ADC and three AAH/AIS lesions. None of the samples had an ALK rearrangement. Patient 3, with two ADC, had different profiles between all three lesions tested. In Patient 6, the ADC had an activating EGFR p.L858R mutation and the synchronous AJH/AIS lesion showed a KRAS p.G12D mutation.

Keywords: synchronous adenocarcinoma, adenocarcinoma in situ, Genomics, Adenocarcinoma

P1.02-079 DNA PLOIDY, CPA4 AND REL B EXPRESSION IN NON SMALL CELL LUNG CANCER: CORRELATION WITH CLINICOPATHOLOGIC PARAMETER

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Background: The aim of this study was to evaluate the expression of CPA4, a member of carboxypeptidase family and Rel B a member of nuclear transcription factor Kappa B family in imprints of resected NSCLC and compare these expressions with DNA ploidy and classical prognostic factors. Methods: A total of 45 smears of patients who underwent surgical treatment for NSCLC were examined immunocytochemically for the expression of CPA4 and Rel B. Imprint smears also were stained using the Feulgen procedure in order to evaluate DNA ploidy in the same cases. Results: Thirty two (71%) of the tumors were classified as aneuploid. CPA4 positive expression was observed in 18 (40%) and Rel B in 21 (46.7%) of the tumors. We found a significant relationship between DNA ploidy and grade (p=0.005). CPA4 and Rel B expression correlated with grade (p<0.001 for both) and also with nodal status (p=0.004 and p=0.017, respectively). Cox regression multivariable analysis demonstrated that CPA4 and Rel B expression were independent prognostic factors. The mean DNA index was higher for tumors with negative expression of CPA4 and Rel B (P=0.045 and p=0.025 respectively). Conclusion: DNA aneuploidy correlates with poor and moderately differentiated tumors. CPA4 and Rel B positive expression is in relation to well differentiated carcinomas and nodal status.

Keywords: NSCLC, DNA ploidy, CPA4, Rel B

P1.02-081 THE RELATIONSHIP OF CDH3 EXPRESSION AND DNA METHYLATION IN THYMIC EPITHELIAL TUMORS

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Background: The genome wide sequence and microarray has performed flourishingly for major cancer specimen in recent day. However, thymic epithelial tumor (TET) was rare tumor comparatively; there are few reports about epigenetic alternation in TET. Cadherin-3, also known as P-cadherin, is a protein encoded by the CDH3 gene. This study was aimed at identifying the relationship DNA methylation and gene expression of CDH3 gene in TET, NSCLC. We evaluated the expression of CDH3 and its promoter DNA methylation levels of cyclin D1 (CCND1), beta catenin (CCNB1), lysyl oxidase (LOX), yes-associated protein-1 (YAP-1), and survivin, with NanoString technology, a new tool for a more accurate expression profiling. KRAS mutations were investigated by pyrosequencing analysis. Clinicopathologic characteristics and survival analysis were available for all patients. Results: Patients under 50 years old (including 50) were defined as the younger group and patients above 50 years old were defined as the older group. Among all the clinicopathologic characteristics, in the younger group there were more women, less solid and more acinar adenocarcinoma prevalent pattern in comparison to the older group. Younger and older groups showed similar survival rates, as well as KRAS mutations frequencies. Also, in the comparison between the gene expression level of the analyzed genes and the two different age subgroups, no statistical difference was found. We then focused on the LKB1 pathway in all series, independently from the age stratification, founding LKB1 low expression associated with low cyclin D1 (CCND1) (p=0.0001), beta catenin (CCNB1) (p=0.0001), and YAP1 (p=0.0024) levels, suggesting a target regulation by LKB1 in order to identify potential target for lung cancer therapy.

Keywords: lung adenocarcinoma, LKB1 pathway, expression analysis

Poster Session 1: P1.02-079 DNA PLOIDY, CPA4 AND REL B EXPRESSION IN NON SMALL CELL LUNG CANCER: CORRELATION WITH CLINICOPATHOLOGIC PARAMETER - Monday, December 5, 2016

Poster Session 1: P1.02-081 THE RELATIONSHIP OF CDH3 EXPRESSION AND DNA METHYLATION IN THYMIC EPITHELIAL TUMORS - Monday, December 5, 2016

P1.02-080 GENOMIC RELATIONSHIP BETWEEN LUNG ADENOCARCINOMA AND SYNCHRONOUS AIS/AAH LESIONS IN THE SAMELOBE

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Poster Session 1: P1.02-080 GENOMIC RELATIONSHIP BETWEEN LUNG ADENOCARCINOMA AND SYNCHRONOUS AIS/AAH LESIONS IN THE SAMELOBE - Monday, December 5, 2016

Abstracts
patients, diagnosed as TET, underwent surgery atTokushima university from 1990 to 2016. 2) DNA was treated by bisulfite conversion. 3) DNA methylation level was measured by in situ methylation assay (Human Methylation 450K DNA Analysis Kit, Illumina) exhaustively. 7 cases of thymic carcinoma and 8 cases of B3 thymoma applied this assay. 4) The methylation levels of CpG sites were calculated as β-values (β = intensity (methylated)/intensity (methylated + unmethylated) by applying default settings of the GenomeStudio Software's DNA methylation module (Illumina). Analysis of this methylation assay used by DNA methylation module (Illumina). Immunostaining was performedEnvision method. It was used Anti-pan-Cadherin (antibody#ab165055), dilution1300 times as first antibody. DAKO ChemMate Envision kit was used as second antibody. Results: CDH3 had 2 CpG islands. 450K methylation assay set 5 CpG sites on first CpG island as promoter region. (CpG sites:B3 thymoma averageβ-values: thymic carcinoma averageβ-values: p-value by t-test=(cg0000242 : 0.070±0.08 : 0.45±0.05 × 2.7±0.070) , (cg00706126 : 0.21±0.21 : 0.55±0.09 : 3.3±0.11) , (cg00748373 : 0.19±0.20 : 0.4±0.07 : 0.01), (cg06575065 : 0.28±0.18 : 0.50±0.07 : 0.02), (cg2747609 : 0.32±0.21 : 0.59±0.09 : 2.02). Immunostaining specimen were classified by scoring system measured by stain intensity and stain expanding. It was classified 2 points;strong, 1 point;weak, 0 point;none, in stain intensity. It was classified 3 points; diffuse>(80%), 2 points;moderate(50-80%), 1 point; focal(20-50%), 0 point;none(20%) in stain expanding. Expression rate(stain intensity point and stain expanding point) defined more than 0 point as expression promotion. Expression promotion rate is 0% in B3 thymoma and 75% in thymic carcinoma. Conclusion: DNA methylation of CDH3 was increasing and P-cadherin protein expression was increasing in thymic cancer compared to B3 thymoma.

Keywords: DNA methylation, thymic epithelial tumor, CDH3
**Abstracts**

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**P1.02-085 MOLECULAR PROFILE IN NSCLC BIOPSY SAMPLES: A MULTICENTER LOCAL STUDY**

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**Background:** During the last time substantial progress have been made in the characterization of the molecular abnormalities of NSCLC tumors such as activations of oncogenes by mutations, translocations and amplifications, which are being used as molecular targets and predictive biomarkers. Currently these molecular analysis is mandatory for therapy selection.

**Methods:** 92 small biopsies and resection specimens of patients with NSCLC (AC) in different institutions of Cordoba were studied during a period (2014-2016). We determined the frequency of molecular alterations in EGFR and gene fusion ALK in our Colombian and Hispanic populations to define the adequate treatment. Histopathology Type, immunohistochemistry (IHC) characteristics as well as molecular profile and several clinical variables were studied. To detect alterations of EGFR and fusion gene EML4-ALK expression, different tests were used with the aim to identify our own profile and make the adequate therapeutic option. EGFR mutation was studied by therascreen kit, PCR, in order to detect genetic alterations in exons 18, 19, 20 and 21. ALK translocations were analyzed by FISH (Vysis- Break Apart, Abbott) and IHC (clon DSF3, ventana, Roche). The molecular profiles were correlated with different clinical variables (age, gender, and tobacco habits).

**Results:** The statistical method used was the multiple regression logistic model. Results: 58 men and 34 women out of 92 samples were tested for EGFR expression. Eight men and ten women expressed EGFR positive. Sixteen men and two women were smokers. Activating kinase-domain mutations in EGFR were identified in 21 pts (22.82%): exon 19 deletion n=11, L858R n=7, exon 20 insertion n=1, other =2. EGFR alterations were related with gender, women showed more alterations of the genes. Age and smoking habit of patients did not show significant association. We used the multiple regression logistic model to correlate EGFR expression to age, gender, tobacco habits. We identified 4 pts (5%) with fusion gene EML4-ALK. ALK alterations were not related to gender, age and smoking habit. Conclusion: Our results showed a comparable relevance of mutations in EGFR and ALK with different clinical variables (age, gender, and tobacco habits).

**Keywords:** mutation, Genomic instability, ATM

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**P1.02-086 ATM MUTATIONS IN LUNG CANCER CORRELATE TO HIGHER MUTATION RATES**

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**Background:** Ataxia telangiectasia-mutated (ATM) is a critical first responder to DNA damage in the cell, but despite being one of the most mutated genes in lung cancer, no specific mutation hotspots have been linked with disease development. Our whole genotypic analysis of ATM protein levels in patient samples suggests that ATM is lost in 20-25% of cases and that this loss correlates with poor overall survival and increased response to adjuvant chemotherapy treatments. We believe that this may be the result of increased genomic instability within the cancer cells caused by a lack of accurate DNA repair. Given that ATM may have higher genetic instability, and that ATM is so highly mutated in lung cancer, we sought to quantify the relationship between ATM mutations and genomic instability, as measured by total somatic mutations. Methods: Using genomic and sequencing data available from the Broad Institute Cancer Cell Line Encyclopedia (CCLE) and the NIH Cancer Genome Atlas (TCGA), we correlated mutations in ATM and other genes involved with the DNA damage response with the total number of mutations annotated in ~900 cancer cell lines and ~500 lung adenocarcinomas. Results: We show that in cell lines across all cancer types, and particularly in lung, breast, and esophageal cancers, mutations in ATM correlate with a significantly higher number of total mutations. Only mutations in the direct damage response genes appeared to associate with total mutations, whereas ps3 – while more commonly mutated – did not correlate with higher mutations in cell lines or patients. In lung cancer patients, ATM mutations were similarly correlated with high somatic mutations. Conclusion: We have identified a potential relationship between ATM mutation and total somatic mutations in cancer cell line and patient tumour genomes, which may be indicative of overall genetic instability. Analysis of the ATM mutations in cell lines and patient samples clearly shows that there are no specific hotspots for mutation in ATM that could allow increased total mutations. Thus screening for ATM mutations alone may not be sufficient to indicate loss of function or instability. However, this data may prove useful in developing panels of targets to screen as mutation hotspots of instability, and ultimately to help identify patients that may benefit from targeted or modified therapy options based on ATM-deficiency or higher genetic instability.

**Keywords:** mutation, Genomic instability, ATM

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**P1.02-087 SENSITIVE DETECTION OF RARE CANCER CELLS BY PREPROGRP-SPECIFIC RT-PCR AND ITS CORRELATION WITH CLINICOPATHOLOGICAL DATA AND SURVIVAL**

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**Background:** Reverse transcription polymerase chain reaction (RT-PCR) based amplification of transcripts expressed in cancer but not in normal non-neoplastic cells is increasingly used for the sensitive detection of rare disseminated or exfoliated cancer cells to improve cancer staging and early detection protocols. This study aimed to detection of Prepro-Gastrin-Releasing Peptide in peripheral blood in lung cancer patients referred to National Cancer Institute, Cairo University, Egypt. And to identify its relationship with clinicopathological features, prognosis and survival.

**Methods:** Our study group consisted of 62 newly diagnosed lung cancer cases and 30 healthy volunteers, RNA was isolated from peripheral blood and then the samples were assayed by nested RT-PCR. Pearson’s chi (X2) test was used to compare categorical variables. Kaplan Meier curves for survival analysis and Median and range for continuous variables were used for statistical analysis. Results: Our study included 62 cases of lung cancer (60 males, median age was 57(34-81) years. For clinicodemographic data (Fig.1). Survival analysis and Median and range for continuous variables were used for statistical analysis. Results: Our study included 62 cases of lung cancer (60 males, median age was 57(34-81) years. For clinicodemographic data (Fig.1). Seventeen (17%) cases had pleural effusion (stage IV). Seventeen (27%) cases had elevated alkaline phosphatase level. Seventeen (27%) out of the 11 cases with bone metastasis underwent splenectomy, internal fixation n bone cement injection to reinforce a bone defect prior to palliative radiotherapy (pRT). As regard SCLC, 10 (16%) cases received platinum based chemotherapy. One case developed Gli3 mucositis and one case developed jaundice and PS became III and shifted to best supportive treatment. One case received gamma knife to cerebellar metastasis, one case received palliative RTH to mediastinum and another pRT to brain before chemotherapy. Twenty-six (41.9%) cases were preprogastrin +ve (53.8% SCLC, 15.4% Squamous cell ca, 15.4% large cell ca, 11.5% adenocarcinoma and 3.8% undifferentiated carcinoma). Median PFS=3.9 months (2.8-4.9). Median
Background: Progress in understanding the pathogenesis of non-small cell lung cancer (NSCLC) led to the development of molecularly targeted agents, including those targeting selected growth factors: vascular endothelial (VEGF), platelet-derived (PDGF), epidermal (EGF), insulin-like I (IGF-1), and anaplastic lymphoma kinase (ALK) signaling. Interestingly, clinical trials of targeted agents and newer chemotherapy regimens have shown that outcomes in histology-based treatment approaches are converging. Consequently, a correct histologic diagnosis is becoming increasingly important. However, even the most careful examination of biopsies by expert pathologists results in misdiagnosis in 10-30% of NSCLCs where histology-based treatment approaches are not specified. Metabolomics is widely used for biomarkers discovery and patients stratification. This novel tool may provide additional diagnostic markers, which could support proper NSCLC subtyping.

In the present study plasma samples obtained from patients with the major NSCLC histological subtypes and controls were analyzed by metabolomics - mass spectrometry (LC-MS) method. The study was performed on the group of 63 NSCLC patients and 32 controls. Based on the histology evidence the patients were classified as ADC (n=20), LCC (n=13), and SCC (n=30). Individuals in all studied groups were matched in age (62±10 years), sex (15-38%), and BMI (26±3). Metabolites extracted from plasma were analyzed by use of LC-TOF-MS in positive and negative ion modes. Metabolic features repeatedly measured in QC samples (RSD >20%) and present in at least 90% of the samples were forwarded to statistical analysis. Depending on data distribution t-test or U-test were used to select metabolites significantly different between controls and NSCLC patients. ANOVA analysis was used to select metabolic subtypes differentiating between NSCLC subtypes. Multivariate analysis was used to search subtype-related patients’ classification. Results: Identification of plasma metabolites significantly different between controls and NSCLC showed differences in phospholipids (e.g. PC 34:3, +53% in NSCLC, p<0.01; PC 36:4, +50% in NSCLC, p<0.001; Lyso PC 18:3 +37% in NSCLC, p<0.02; PE 34:2, +34% in NSCLC, p<0.0002) and docosahexaenoic fatty acid (34% in NSCLC, p<0.02). Based on metabolites significant after ANOVA analysis it was possible to build good quality (R²=0.652, Q²=0.408) partial least square discriminant analysis (PLS-DA) model separating NSCLC patients. Among metabolites responsible for this separation sphinganine (p<0.009), anandamide (p<0.009), malonyl carnitine (p<0.001), and Lyso PE 20:5 (p<0.02) were mentioned. Conclusion: Metabolic fingerprinting of plasma samples allowed for selection a panel of metabolites able to discriminate between NSCLC subtypes. Although promising, obtained results require further validation with target methods and on larger cohort of patients.

Acknowledgements: The study was funded by National Science Centre, Poland (2014/13/B/NZ5/01256).

Keywords: NSCLC subtypes, plasma metabolic fingerprinting, LC-MS-based metabolomics

Poster Session 1 - P1.03: Radiology/Staging/Screening

Monday, December 5, 2016

P1.03-003 THE WARBURG EFFECT: PERSISTENCE OF STEM CELL METABOLISM IN LUNG CANCER AS FAILURE OF DIFFERENTIATION

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Background: Two recent observations are relevant to explaining Warburg’s observation the cancers constitutively utilize glycolysis in the presence of oxygen sufficient for oxidative phosphorylation. First, the metabolism of stem cells has been shown to be constitutive (‘aerobic’) glycolysis, with differentiation involving a transition to oxidative phosphorylation. Second, the degree of glucose uptake by a cancer has been associated with histologic differentiation. We hypothesized that the high levels of glucose uptake observed in poorly differentiated lung cancers may reflect persistence in cancers of the glycolytic metabolism of stem cells that fail to fully differentiate. Methods: Tumor glucose uptake was measured by FDG-PET in 839 patients with histologically diverse cancers including NSCLC. We used normal mixture modeling to explore SUV distributions and tested for association between glucose uptake and histologic differentiation, risk of lymph node metastasis, and survival. Using microarray data, we performed pathway and transcription factor analyses to compare tumors with high/low
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significant difference in the successful use of percutaneous lung biopsy with CMS-46 and CMS-50 for 50-gene (CMS-50) assessment. The success rate was 1.87 cm (0 to 8.5 cm). 48.70% of the biopsies had local hemorrhage during three months prior to the procedure. Average lesion distance from the pleura was 6.50 cm (0.8 – 15.6). 84.91% of the lesions were spiculated, 78% were solid and 4.74% had calcification. 20.69% of the patients had pleural effusion, 65.52% had history of smoking, 89.22% of the tumors biopsied were primary lung cancer and 10.78% were lung metastasis from lung cancer. Average lesion size was 4.07 cm (0.8 – 15.6). 84.31% of the lesions were spiculated, 78% were solid and 4.74% had calcification. 20.69% of the patients had pleural effusion, 65.78% had known metastasis and 20.75% had systemic treatment within three months prior to the procedure. Average lesion distance from the pleura was 1.87 cm (0 to 8.5 cm). 48.70% of the biopsies had local hemorrhage during the procedure, 18.10% developed pneumothorax and 5.17% needed a chest tube. 44 biopsies were collected for NGS with 46-gene multiplex platform (CMS-46) and 188 for 50-gene (CMS-50) assessment. The success rate was 59.09% for CMS-46 and 80.85% for CMS-50 (p=0.0048). Conclusion: There is a significant difference in the successful use of percutaneous lung biopsy with two different NGS platforms.

Keywords: Percutaneous lung biopsy, next generation sequencing, lung cancer

**POSTER SESSION I - P1.03: RADIOLoGY/STAGING/SCREENING
BIOLOGY – MONDAY, DECEMBER 5, 2016

**P1.03-005 HIGH RESOLUTION METABOLOMICS IN DISCOVERING PLASMA BIOMARKERS OF LUNG CANCER PATIENTS WITH EGFR COMMON MUTATIONS (EXON 19 OR 21)**

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Background: The epidermal growth factor receptor (EGFR) is a key target in the treatment of advanced non-small cell lung cancer (NSCLC). The presence of EGFR mutations predicts the sensitivity to EGFR tyrosine kinase inhibitors (TKIs) of NSCLC patients. For this reason, EGFR mutation test is required to provide personalized treatment options. Currently available DNA sources are mainly small biopsies and cytological samples, providing limited and low-quality material. So, there is the need of new biotyper discovery. Recently, metabolomics, which is the comprehensive study of low molecular weight metabolites, has also been developed. Integration of transcriptomic and metabolomic data has enabled deeper analysis of chemosensitive pathways. In this regard, this study aims to apply high resolution metabolomics (HRM) to detect significant compounds that might contribute in inducing EGFR mutations. Methods: Plasma samples from 2 healthy volunteers and 15 lung cancer patients were analyzed to detect biomarkers which can predict EGFR mutations. The comparison was made between healthy control and lung cancer groups for metabolic differences. Ten patients had EGFR mutations and five patients had wild type EGFR (n=5) in tumor tissue. The EGFR mutation group was divided into exon 21 deletion group (n=5), and exon 19 deletion group (n=4). Differences in metabolic profiles of EGFR mutation lung cancer populations and EGFR wild type lung cancer patients were examined. Metabolites were separated using Agilent 1200 High Performance Liquid Chromatography and Agilent 6530 quadrupole time-of-flight LC/MS. Results: From 216 metabolites, 112 metabolites were found to be significantly different. Relative concentration of L-valine, Linoleate, tetradecanoyl carnitine, 5-MTHF, and N-succinyl-L-Glutamate-5-semialdehyde showed significant difference (p<0.05). Linoleic acid was elevated in mutation group while tetradecanoyl carnitine was found to be lowered in mutation group. These two compounds are related to the alteration of mitochondrial energy metabolism (carnitine shuttle). Compounds related to amino acid metabolism, L-valine and N-succinyl-L-Glutamate-5-semialdehyde were increased in mutation group. Conclusion: Our results show that HRM with the combination of pathway analysis from significant metabolites was able to discriminate an EGFR mutation positive patients (exon 19 or exon 21) from wild type advanced NSCLC patients. Therefore, high-resolution metabolomics can be the potential non-invasive tool to utilize clinically to detect the EGFR mutations in NSCLC patients.

Keywords: EGFR mutation, NSCLC, metabolomics, High resolution metabolomics

**POSTER SESSION I - P1.03: RADIOLoGY/STAGING/SCREENING
BIOLOGY – MONDAY, DECEMBER 5, 2016

**P1.03-006 QUANTIFICATION OF PD-L1 EXPRESSION ON TUMOR CELLS IN NON-SMALL CELL LUNG CANCER USING NON-ENZYMATIC TISSUE DISSOCIATION AND FLOW CYTOMETRY**

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Background: Tumors use many mechanisms to evade the immune system, often manipulating pathways to evade cell death. The PD-L1/PD-1 pathway in particular, has become a promising target for immuno-oncology drug development. PD-L1/PD-1 therapy has been shown to be effective in patients with NSCLC, regardless of their PD-L1 expression profile by immunohistochemistry. This creates a challenge in determining potential responders from non-responders prior to treatment. The objective of this study was to develop a trulyquantitative technology for PD-L1 expression in NSCLC. In addition, we also present a non-enzymatic technology that creates a tumor cell suspension from fresh tumor tissue so that either FNA or fresh tissue can be used. Methods: 4 mm punches were taken from each tumor.

Keywords: EGFR mutation, NSCLC, metabolomics, High resolution metabolomics

**POSTER SESSION I - P1.03: RADIOLoGY/STAGING/SCREENING
BIOLOGY – MONDAY, DECEMBER 5, 2016
Non-enzymatic tissue homogenization (InCellPREP; IncellDx, CA) was performed. Cells were labeled with antibodies directed against CD45 and PD-L1, fixed and permeabilized then stained with DAPI to identify intact, single cells, and to analyze cell cycle. Results: We compared PD-L1 expression by flow cytometry using a 1% cut-off for positivity in the tumor cell population and a 1% cut-off of cells with at least 1 intensity in immunohistochemically stained tissue sections as positive (Table 1). As demonstrated in the table, 10 of 12 lung tumor samples were discordant while 2 were discordant, one positive by flow and negative by HC and one negative by flow and positive by IHC. PD-L1 expression by flow cytometry varied widely (1.2% to 89.4%) even in the positive discordant cases. In addition, PD-L1 expression in the aneuploid tumor population did not necessarily agree with the expression in the diploid tumor population.

Conclusion: Fine, unequivocal, quantification of PD-L1 on tumor and immune cells in NSCLC may allow for better prediction of response to therapies. The present study also offers a technology that can create a universal sample type from either FNA or fresh tissue.

Keywords: PD-L1, Immunotherapy, NSCLC, diagnostic

POSTER SESSION 1 - P1.03: RADIOLGY/STAGING/SCREENING
Biology, Monday, December 5, 2016

P1.03-007 IMPROVEMENT IN PERFORMANCE OF AN AUTOANTIBODY PANEL TEST FOR DETECTION OF LUNG CANCER BY ADDITION OF A SINGLE NOVEL BIOMARKER (EDB1)
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Background: In order to provide optimal cost-benefit, the US national lung cancer screening program is restricted to a relatively narrow group of high risk individuals, with 70% of patients with lung cancer falling outside the CT screening inclusion criteria. Additional tests that can identify those at increased risk who do not qualify for CT screening may be useful. A biomarker assay that measures a panel of autoantibodies is intended to be used as an aid to early detection of lung cancer is commercially available. It has high specificity but moderate sensitivity. The aim of this study was to investigate the performance of an additional biomarker that may increase the sensitivity for detection of lung cancer by running a single biomarker (EDB1) in combination with the autoantibody test.

Methods: The validation studies provided the performance data and high specificity in both control groups (risk matched and inflammatory/biomarker (EDB1) that demonstrated clear cancer/normal differentiation. The discovery screen identified one protein biomarker (EDB1) that demonstrated clear cancer:normal differentiation and high specificity in both control groups (risk matched and inflammatory/autoimmune disease). The specificity of EDB1 in patients with benign autoimmune disease was 97.8%.

Conclusion: Running a single biomarker (EDB1) in combination with the autoantibody test improves the sensitivity for detection of lung cancer by between 10% and 25% with minimal adverse effect on specificity so maintaining the PPV of the test.

Keywords: biomarker, autoantibody panel, lung cancer

POSTER SESSION 1 - P1.03: RADIOLGY/STAGING/SCREENING
Pneumonology, Monday, December 5, 2016

P1.03-008 CLINICAL IMPORTANCE OF INDOLENT LUNG CANCERS
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Background: The occurrence and importance of “indolent” lung cancers is intensely discussed. In the National Lung Cancer Study Trial (NLST) (1) it was estimated that 18% of all cancers were indolent (2). This was based on comparison with the controls being “the golden standard”, i.e. assuming that there were no indolent cancers among those. However, studies in the 20th century with X-ray screening for lung cancers showed the incidence of indolent tumors to be around 25% in such materials. Methods: We have made some calculations of the NLST material based on the difference in numbers of lung cancers found at the first screening and the subsequent yearly ones. Results: Simple estimation: the 5 year “normal” survival of all lung cancers is 16%; in the NLST X-ray arm only (the controls) it was 53%. If 25% is due to indolence, 12% (53 minus 16 minus 25) must be due to selection. In the screened arm (low CT), 66% cent were alive, and thus, 38% (66 minus 16 minus 25) must be due to indolent cancers. A sophisticated calculation: The difference in numbers of discovered cancers at first and following screenings in the screened arm only (thus disregarding the controls) can be used to give an indication of the proportion of indolent cancers. This will also result in a percentage of indolent cancers of around 40. Conclusion: Screening for lung cancer with low-dose CT has been proven to save lives. However, this comes with the risk of doing more harm than good to those who actually have an indolent cancer. Of all confirmed and staged patients in the CT arm of the NLST, 70 per cent were stage I and II, and almost all of them had surgery. The indolent cancers would be included among these, and if 30% of all cases they will amount to two thirds of the operated patients. Hopefully, new studies might make it possible to discriminate between indolent and life-threatening tumors. In the meantime, we should choose therapies with as little side effects as possible, even if these methods do not maximize the possibility of cure. 1. National Lung Cancer Screening Trial Research Team. Reduced lung cancer mortality with low-dose computed tomography screening. New Engl J Med 2011; 365:395-409. 2. Patz EF, Pinsky P, Gatsonis et al. Over-diagnosis in low-dose computed tomography screening for lung cancer. JAMA Int Med 2014; 174:269-274.

Keywords: survival, Indolence, indolent lung cancers, Screening

POSTER SESSION 1 - P1.03: RADIOLGY/STAGING/SCREENING
Pneumonology, Monday, December 5, 2016

P1.03-009 VENOUS THROMBOEMBOLISM (VTE) IN LUNG CANCER - ASSOCIATIONS AND PROGNOSTIC ROLE: RESULTS OF A PROSPECTIVE COHORT STUDY FROM NORTH INDIA
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Background: Venous thromboembolism (VTE) in cancer remains an under- 
evaluated and under-diagnosed entity. This prospective study aimed to 
assess VTE incidence, risk factors for its occurrence and its effect on overall survival (OS) in a cohort of lung cancer (LC) patients at diagnosis and during first-line chemotherapy. Methods: Over a 1-year period (July 2014-June 2015), 301 patients with histology-proven LC were screened for deep venous thrombosis (DVT) with compression ultrasonography and for pulmonary thromboembolism (PTE) with CT pulmonary angiography and diagnosis after four cycles of chemotherapy. Patient demographics, comorbidities, presenting symptoms of VTE events, treatment details and outcomes were noted. Logistic regression and Cox proportional hazard analyses were done to determine factors associated with VTE occurrence and OS respectively. Results: Most patients had advanced disease (G1.2% Stage IV, 31.3% stage IIIb). Overall, 16/301 patients (5.3%) had VTE (DVT alone (n=5), PTE alone (n=2) and DVT with PTE (n=9) with incidence rate of 90 per 1000 person-years. Median duration from LC diagnosis to VTE event was 96 days. All DVT episodes were asymptomatic. PTE events were symptomatic in 72.7% and mass (attributable hypotension) in 36.4% for which thrombolysis was done. VTE treatment was associated with minor bleeding in 3 patients but no major bleeding occurred. Age, COPD (odds ratio (OR) = 5.2), ECOG PS ≥ 2 (OR=3.1), and number of extrathoracic metastatic sites (OR=1.9) were independent risk factors for VTE on multivariable logistic regression analysis. No association was observed with histology, EGFR mutation status, other comorbidities or baseline biochemical tests. Chemotherapy regimens, number of chemotherapy cycles and radiological responses were similar amongst patients with and without VTE. Median OS was significantly less in VTE patients [161 (95% CI = 79-243) vs. 311 (95% CI = 270-425) days; p=0.007] with death attributable to VTE in 50%. On multivariable Cox proportional hazard analysis, VTE (hazard ratio (HR) = 2.1 (95% CI = 1.1-3.8)) was independently associated with poor OS as were smoking (HR = 1.7 (95% CI = 1.2-2.7)), ECOG PS = 2 (HR = 1.6 (95% CI = 1.1-2.3)) and serum albumin (continuous variable HR = 0.6 (95% CI = 0.4-0.8)). Conclusion: VTE occurs in approximately 5% of newly diagnosed LC patients, is associated with inherently poor prognostic factors (COPD, ECOG PS=2, hypoaluminaemia and extent of metastasis) and with worse OS independent of other variables. Since all DVT episodes are asymptomatic, compression ultrasonography remains the preferred mode for cost-effective initial evaluation of suspected VTE in developing countries.

Keywords: venous thromboembolism, risk factors, overall survival, Incidence

Poster Session 1: P1.03: Radiology/Staging/Screening

P1.03-010 Characteristics of Lung Cancer Patients Diagnosed Following Emergency Admission

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Background: The proportion of patients with cancers diagnosed via the emergency route and their demographic characteristics vary according to tumour type. Patients with lung cancers diagnosed as emergency presentations suffer worse outcomes(2). The aim of this observational study was to determine the characteristics of a sample of patients with new lung cancers presenting through the emergency route. Methods: Clinical and demographic patient data were extracted from the London Cancer Registry. Data relating to emergency presentations of lung cancer were collected prospectively between January and August 2013 from nine acute trusts across the corresponding time frame from the National Lung Cancer Audit data (NLCA). Results:

From the NLCA, there were an estimated 964 lung cancers recorded within the London cancer region during the study period. Of these, 310 (32%) lung cancers were recorded in the London Cancer registry as having presented via the emergency route. The median age of these patients was 73. The majority of patients were white and from areas of increased social deprivation. The proportion of patients presenting with stage IV disease was 67%, while 58% had a performance status of 0-2. The most common presenting symptoms were respiratory. 95% of patients were treated with palliative rather than curative intent. Conclusion: A prospective study of new lung cancers within London Cancer are diagnosed following emergency admission. The next phase of work includes incorporating results from the London Cancer Alliance to provide pan-London data and to develop tools in primary care to identify these patients prior to emergency admission.

Keywords: emergency presentation, routes to diagnosis, socioeconomic deprivation

Poster Session 1: P1.03: Radiology/Staging/Screening

P1.03-011 Clinical Characters of 19 Bronchial Asthmatic Patients with Lung Cancer

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Background: To investigate the clinical features of lung cancer among asthmatic patients. Methods: Retrospectively analyzed the clinical characteristics of 19 patients with bronchial asthmatic and lung cancer that were treated by the second hospital of Jilin university from 2009 to 2015. Results: The morbidity of lung cancer in bronchial asthma patients accounted for 1.4% of the patients in our hospital. All patients were older than 40 years old, among which 11 (58%) were over 60. Cough and expectoration were the major clinical symptoms which occurred in 14 cases (74%). According to the pathological results, 4 cases were squamous cell carcinoma (21%), 7 were small cell carcinoma (37%), 7 were adenocarcinoma (37%), and only 1 case were poorly differentiated non-small cell carcinoma (5%). In the small cell lung cancers, the primary cancer in 5 cases were still at limited stage, in 2 cases had developed into a extensive tumor. In non small cell lung cancers, there were 2 cases at stage IIA, 1 case at stage IIIB, 1 case at stage IIB and 1 case at stage IV. From the chest CT performance, the patchy and mass like nodules were recognized as the main manifestations. In all the 19 patients, manifestations of asthma were not effectively managed. In 10 of the patients, the PS score was poor and did not receive any anti tumor treatment, while other 9 cases received anti tumor therapy. Conclusion: Bronchial asthma, especially those being not well controlled, is a potential risk factor for lung cancer. Lung cancer should be awared in the acute episode of asthma. For
asthma exacerbation in patients over 60 years old, the chest CT scan is a recommended choice, or regularly reviewed by low dose CT screening to discover lung cancer at early stage and improve prognosis. But the anti tumor therapy of severe asthma combined with lung cancer patients is still a difficult problem.

Keywords: clinical characters, asthma, lung cancer

POSTER SESSION 1 - P1.03: RADIOLOGY/STAGING/SCREENING
Radiology – MONDAY, DECEMBER 5, 2016

P1.03-012 EXPERIENCE WITH BIOSENTRY(TM) TRACT SEALANT SYSTEM FOR PERCUTANEOUS CT-GUIDED LUNG NODULE BIOPSIES IN AN ONCOLOGY POPULATION
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Background: Tract sealants are being used more frequently to reduce pneumothoraces and chest tube placement in patients undergoing lung biopsy. Use of a sealant plug can produce visible biopsy tracts on follow-up imaging and can mimic the appearance of malignant tract seeding. The purpose of our study was to characterize these tracts and determine the likelihood of malignant seeding to inform further management including localized radiation therapy and/or surgical planning. Methods: Over a 15 month period 407 lung biopsies were performed in patients with known or suspected thoracic and extrathoracic malignancies using a BioSentry Tract Sealant System; 321 cases had follow up CT studies. 4 chest radiologists retrospectively analyzed subsequent imaging to determine the incidence, appearance, temporal relationship and evolution of biopsy tracts. Tracts that decreased or did not change on follow-up were considered benign. 10 surgically resected cases were retrospectively examined by a pathologist for malignant tract seeding. Results: 321 cases were analyzed. 237 (74%) had a visible biopsy tract on CT (95% CI 0.69, 0.78) (primary lung cancer n=80, metastases n=81, benign nodule n=66). All tracts were identified on 1st follow-up imaging at 1-3 months post-biopsy. Tracts were typically serpiginous and smooth or lobulated with a thickness of 2-5 mm. 218/237 (92%) tracts were unchanged over time (mean follow up, 12 months). 15/237 (6.3%) decreased in thickness. Unchanged or decreasing tracts were considered negative for malignant seeding. Increase in tract thickness or nodularity occurred in 4/237 (1.8%), suspicious for malignant tract seeding. 0/90 (0%) biopsy tracts in primary lung cancer showed progressive increase. 4/81 (4.9%) tracts in patients with metastases showed increase (mean, 59 days post-biopsy). 10 recently resected nodules (5 primary NSCLC, 5 metastases) had no malignant tract seeding at histology. Conclusion: An observable biopsy tract on CT is common after lung biopsy using the BioSentry11 device. Tracts from biopsy of primary lung cancers using the BioSentry device had no malignant seeding and they should have no impact on surgical resection or localized radiation therapy. In the study population, patients who underwent lung biopsy for metastasis had a higher than expected rate of malignant seeding manifested by increase in tract thickness over time, requiring further investigation.

Keywords: biopsy tract, Lung biopsy, Malignant tract seeding, biopsy tract sealant

POSTER SESSION 1 - P1.03: RADIOLOGY/STAGING/SCREENING
Radiology – MONDAY, DECEMBER 5, 2016

P1.03-013 DIAGNOSIS, ASSESSMENT AND PREDICTION OF EARLY RESPONSE TO CHEMOTHERAPY BY USING DIFFUSION-WEIGHTED MRI IN LUNG CANCER
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Background: Radiographic screening, diagnosing, staging, and assessing procedures with ironizing radiation-based tests are currently most widely used for lung cancer. However, one of the major harms of these imaging tests is the potential for radiation-induced carcinogenesis. Whether radiographic screening, diagnosing, staging, and assessing procedures increase cancer incidence and death in patients exposed to radiation of medical sources is ignored in the context of indefinite answer. We aimed to evaluate the ability of radiation-free diffusion-weighted magnetic resonance imaging (DW-MRI) to diagnose, assess and detect early response to chemotherapy in lung cancer patients. Methods: This study was approved by the institutional review board, and written informed consent was obtained from all patients. Ninety patients with lung cancer as confirmed by pathologic examination (25 women, 65 men; mean age, 57 years) who underwent chemotherapy were enrolled between November 2014 and October 2015. All patients underwent MRI and computed tomography (CT), as the reference test, at baseline and after the second course of chemotherapy. The apparent diffusion coefficient (ADC) of each lung carcinoma was calculated from images. Ki-67 scores and tumor markers in the serum, carcinoembryonic antigen (CEA), neuron-specific enolase (NSE) and squamous cell carcinoma antigen (SCC), were determined. ADC values were compared among different histopathologic types and between pretreatment and posttreatment. Receiver operating characteristic (ROC) analysis was performed to evaluate the diagnostic performance of ADC and its combination with tumor markers. The relationship between the baseline ADC values with Ki-67 scores and final tumor size reduction were analyzed by using the Pearson correlation coefficient. This study is registered with Clinical Trials.gov (NCT02320677). Results: Before treatment, there were significant differences between NSCLC and SCC (P=0.000), adenocarcinoma and SCC (L=0.000), and squamous cell carcinoma and SCC (P=0.002). ADC values and Ki-67 score showed negative correlation (r=-0.408, P=0.000). In the pretreatment analysis, area under curve (AUC) of the combination of CEA, SCC and NSE was 0.772, 0.821 and 0.761, respectively. ADC values were significantly different between pretreatment and posttreatment (P=0.001), and partial response (PR) and stable disease (SD) groups. ADC at baseline was negatively correlated with tumor size reduction (r=-0.434, P=0.017). As well, AUC of ADC at baseline to discriminate PR and SD groups was 0.804. Conclusion: Our findings extended the previous findings by that ADC in DW-MRI could: (1) discriminate different histopathologic types; (2) evaluate the malignancy; (3) predict and monitor the early response to chemotherapy. Radiation-free DW-MRI seems to be a promising tool for management of lung cancer.

Keywords: lung cancer, diffusion-weighted magnetic resonance imaging, diagnosis, chemotherapy

POSTER SESSION 1 - P1.03: RADIOLOGY/STAGING/SCREENING
Radiology – MONDAY, DECEMBER 5, 2016

P1.03-014 VALUE OF PERFORMING FINE NEEDLE ASPIRATION WITH CORE BIOPSY FOR GENOMIC MUTATION ASSESSMENT IN PERCUTANEOUS LUNG BIOPSY
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Background: Personalized care of lung cancer patients requires determination of targetable genetic mutations. This study was performed to investigate the added value of performing fine needle aspiration (FNA) with core biopsy in lieu of FNA alone for molecular testing of lung cancer patients. Methods: Retrospective analysis of all CT-guided lung biopsies in lung cancer patients with samples sent for next generation sequencing (NGS) with a 50-gene multiplex panel during 2013 and 2014. Procedures were performed using 19 gauge coaxial guides, 20 gauge side-cutting core needles and 22 gauge Chiba needles. Samples were processed for histological evaluation. The remaining material was reviewed for adequate tumor cellularity (≥20%) by pathology. If the specimen collected through core biopsy did not present adequate tumor cellularity, the FNA material was reviewed and sent for mutation analysis. DNA was extracted and sequenced with a 50-gene multiplex platform (Ion Torrent Personal Genome Machine). If the samples were not adequate for FNA, single gene sequencing was performed for the requested genetic mutations. Patient demographic, lesion imaging features, procedure technique and molecular results were collected. Descriptive statistics were tabulated. Results: A total of 188 patient met the criteria for this study. 184 patients had FNA and core biopsy together and 4 had only FNA. 19 out of 184 (10.32%) core biopsy specimen had <20% tumor cellularity. 19 out of 184 (10.32%) core biopsy specimen had <20% tumor cellularity. 10/184 (5.45%) patients did not have adequate tumor cellularity from FNA. Of the 174 patients with adequate tumor cellularity, 156 patients had actionable genetic alterations identified on NGS, and 94 patients (54.1%) had ≥1 actionable genetic alteration. 78 patients (44.7%) had only FNA. 19 out of 184 (10.32%) core biopsy specimen had <20% tumor cellularity. 10/184 (5.45%) patients did not have adequate tumor cellularity from FNA. Conclusion: The addition of FNA to core during percutaneous lung biopsy increased the incidence of actionable genetic mutations identified by NGS.

Keywords: clinical characters, asthma, lung cancer
Abstracts

POSTER SESSION 1 - P1.03: RADIOLOGY/STAGING/SCREENING
RADIOLOGY - MONDAY, DECEMBER 5, 2016

P1.03-015 ASSESSMENT OF RESPONSE OF FDG-PET USING TOTAL LESION GLYCOLYSIS (TLG) IN NSCLC PATIENTS TREATED WITH NIVOLUMAB: RESULTS OF A PILOT STUDY
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Background: Recent studies using FDG-PET measure the total volumes of the FDG-avid lesions to represent the whole body total metabolic tumor volume (MTV) demonstrating a prognostic significance in NSCLC. Total lesion glycolysis (TLG) is the product of mean SUV and MTV and studies have shown the usefulness of TLG for evaluating treatment response. We decide to preliminarily explore the role of TLG, which combines the volumetric and metabolic assessment, as a predictor of response to nivolumab in NSCLC patients and to determine whether in these patients TLG could provide a better evaluation of response when compared to RECIST.

Methods: Between September 2015 and April 2016, we enrolled 15 previously treated advanced NSCLC patients to receive nivolumab 3 mg/kg q2w. The CT-scan and FDG-PET evaluation were performed before starting therapy and after 8 weeks (early evaluation). We compared responses assessed by CT-scan and FDG-PET at 8 weeks according to RECIST 1.1 and TLG parameter respectively. We also performed a CT-scan at 12 weeks to confirm or refute the results of the assessment at 8 weeks. Results: There are no standard cut-offs for the TLG parameter. A ROC curve was used to obtain thresholds for the TLG criteria. The ROC study suggested a TLG value between -76% and +76% to define an SD. We considered a TLG value above +76% to define a PD, while a TLG inferior to -76% was necessary to define a PR. In one patient the evaluation at 8 weeks according to TLG criteria showed PD. The same patient presented SD according to RECIST assessed by CT-scan at 8 weeks. For this patient CT-scan at 12 weeks confirmed PD. In this case the TLG of the FDG-PET early identified the patient’s progression better than CT-scan. In other two patients, TLG criteria assessed at 8 weeks identified a PR in contrast with SD according to RECIST assessed by CT-scan at 8 weeks. CT-scan at 12 weeks confirmed PRs for both these patients. Even in this two cases the evaluation of TLG by FDG-PET early recognized patient’s responses better than CT-scan.

For the remaining 12 patients no differences in terms of responses were observed between RECIST and TLG criteria at 8 weeks when compared to RECIST assessed by CT-scan at 12 weeks. Conclusion: These preliminary results from this small study suggest that TLG criteria could provide an early identification of response to nivolumab in NSCLC patients.

Keywords: FDG-PET, RECIST, Nivolumab, total lesion glycolysis

POSTER SESSION 1 - P1.03: RADIOLOGY/STAGING/SCREENING
RADIOLOGY - MONDAY, DECEMBER 5, 2016

P1.03-017 DOES PET/CT SUVMAX VALUE CORRELATE WITH LONG-TERM SURVIVAL IN PATIENTS WITH SURGICALLY TREATED STAGE I NON-SMALL CELL LUNG CANCER
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Background: Positron emission tomography (PET/CT), which detects the biologic activity of tumor cells is routinely used in staging of non-small cell lung cancer (NSCLC). However, the role of PET/CT in predicting disease free and long-term survival of surgically treated stage I NSCLC is not clear. In this study, we aimed to investigate prognostic value of metabolic uptake (SUVmax) of the tumor in patients with surgically treated stage I NSCLC.

Methods: Two-hundred and sixty patients who had preoperative PET/CT and pulmonary resection for stage I NSCLC between 2005 and 2015 were included into study. The patients were divided into four groups according to the SUVmax value, 0-5, group 1, 5-10 group 2, 10-15 group 3, and over 15 group 4. Lung resection, segmentectomy/lobectomy, was performed within 30 days of PET/CT in all patients. Tumor SUVmax and other potential prognostic variables were chosen for analysis in this study. Patients univariate and multivariate analyses were conducted to identify prognostic factors associated with long-term survival. Results: There were 53 females and 207 males with a mean age of 61.5 (range 20-84). The mean SUVmax value of the tumors in PET/CT was 10.1 (1-48). The type of the lung resection was segmentectomy in 33 (12.2%), and lobectomy in 227 (87.3%). Pathologic staging of the tumors was stage 1A in 156 (60%), and stage 1B in 104 (40%). Median follow-up time was 44 months, and overall 5 year survival rate was 81.7% and there was not any statistically significant difference between the groups (p=0.3). SUVmax value of the tumor was not affected by age, gender, tumor type and location.

Conclusion: Although the previous studies revealed correlation between SUVmax values and impaired long-term survival, this study revealed no correlation between SUVmax values and long term survival in patients with surgically treated stage I NSCLC. However, tumors with higher SUVmax values have higher chance of perineural invasion. Further studies for possible relationship between metabolic activity and histopathologic characteristics of the tumors are warranted.

Keywords: lung carcinoma, PET CT, Prognosis

POSTER SESSION 1 - P1.03: RADIOLOGY/STAGING/SCREENING
RADIOLOGY - MONDAY, DECEMBER 5, 2016

P1.03-018 FDG-PET/CT IN PATIENTS WITH EGFR-MUTATED NSCLC TREATED WITH TKI. CAN WE IDENTIFY EARLY LESIONS AT HIGHER RISK OF PROGRESSION?
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Background: Two-dimensional CT measurement considered unreliable in the evaluation of small pulmonary nodule less than 2 cm, and a nodule less than 1 cm in diameter considered non-measurable according to RECIST criteria. The aim of this study was to determine the accuracy of visual assessment on the growth of immeasurable small pulmonary nodules less than 1 cm in diameter on CT. Methods: We selected 125 CT images (1-mm slice thickness axial images, lung window setting, lung algorithm) which have a small pulmonary nodule less than 1 cm. Then, we magnified the pulmonary nodules to 120% in diameter using the Photoshop. We coupled these images to 125 sets of ingrowth and growth groups, respectively. Four radiologists with varying experience read these sets to five-point scale using visual assessment (definitely ingrowth, probably ingrowth, possibly growth, probably growth, and definitely growth). Results: The areas under the receiver-operator characteristic curves of visual assessment on growth of small pulmonary nodules were 0.975 for observer 1, 0.986 for observer 2, 0.989 for observer 3, and 0.913 for observer 4, respectively. Sensitivities were 96.0% (120/125), 98.4% (123/125), 98.4% (123/125), and 88.0% (110/125), respectively. Specificities were 99.2% (124/125), 98.4% (124/125), and 98.6% (121/125), respectively.

Conclusion: Visual assessment showed high diagnostic performance for determining growth of non-measurable target pulmonary nodules with 20% increase in diameter.

Keywords: pulmonary nodule, visual assessment, CT
Eighty-nine lesions from 13 caucasian EGFR-mutated NSCLC patients treated with TKI were analyzed. Date of progression for each lesion was collected. SUVmax, Metabolic Tumor Volume (MTV), Total Lesion Glycolysis (TLG) were measured on baseline and early follow-up PET/CT performed 2-3 months later. Variations between the 2 PET/CT (SUVmax, MTV, TLG) were calculated. Medians were used as cut-off values for statistical analysis. Risk of progression was analyzed according to PET/CT parameters and Odds Ratios (OR) were calculated. Results: The best metabolic predictors of progression were high MTV (OR=4.3, p<0.001), high MTV (OR=8.3, p<0.001) and high TLG (OR=6.9, p<0.001). On the early follow-up PET/CT, SUVmax 97.6% (OR=3.9, p=0.02) was also associated with early progression. Conclusions: Lesions with complete, partial and no response on early follow-up PET/CT were excluded from the study. Date of progression for each lesion was collected. SUVmax did not predict the overall extent or any specific pathway of glucose metabolism. SUVmax did not correlate with any metabolic flux parameters including lactate. Figure 1

Conclusion: Although all FDG-PET-positive tumors metabolized glucose, the SUVmax did not predict the overall extent or any specific pathway of glucose metabolism. TV predicts a propensity to consume alternative fuels, such as lactate, in addition to glucose.

Keywords: Response to Treatment, Tumor Metabolism, Staging, PET scan
Background: There has been a great advancement in understanding natural history of ground-glass opacity (GGO), which represents histological lepidic growth in early stage pulmonary adenocarcinoma. Among them, some GGO lesions reveal invasive growth related to obvious on consolidation on thin-section computed tomography (TSCT), i.e., GGO with semi-consolidation. However, little is known regarding clinicopathological and radiological relationship of this new entity. Methods: During 2004 and 2016, we underwent AAA (2327) surgical resections for clinical-stage I/A lung adenocarcinoma. Among them, 286 (12.3%) GGO lesions without any consolidations were identified based on the findings on TSCT. They were categorized into two groups; pure-GGO (PG) and GGO with semi-consolidation (SC) according to the radiological findings. Semi-consolidation is defined as GGO with increased homogenous density without consolidation on TSCT. Clinicopathological and radiological factors were analyzed between these two groups. 

Survivals were calculated by Kaplan-Meier estimation methods. Results: Of the cases, 172 (60.1%) showed PG and 114 (39.8%) showed SC. Significant or marginal differences were clinically observed between PG and SG groups regarding age (53.4 ± 63.0, p=0.02), pack-year smoking status (10.2 ± 11.6, p=0.084), tumor size (12.2cm vs. 13.9cm, p=0.06), respectively. Noninvasive lesions including atypical adenomatous hyperplasia, adenocarcinoma in situ or minimally invasive adenocarcinoma were observed in 144 patients (83.7%) of PG and 74 (64.9%) of SC, however, the frequency of invasive adenocarcinoma or lymph-vascular invasions were significantly higher in SC group compared to PG group (15.7% vs 33.9%, p<0.001; 4.3% vs 0.5%, p=0.040) despite their GGO appearances. There was no lymph node metastasis in both PG and SC groups. Overall lung-cancer specific survival is 100% to date in both PG/SC groups with mean follow-up period of 97months. Conclusion: Despite the conventionally same category as a native GGO appearance on TSCT, invasive adenocarcinoma was frequently observed in radiologically dense GGO lesions, indicating that PG might progress to SC over time. Surgical outcome for both groups are excellent. Therefore, more studies regarding optimal surgical procedures and long-term outcome of these two groups should be warranted.

Keywords: Adenocarcinoma, ground glass opacity, lung cancer imaging
where \( k \) is the rate constant of elimination. The biological half-life was investigated in 7 patients with lung cancer. Methods: First, serum KL-6 levels were measured using the electrochemiluminescence immunoassay method. The cut-off level of 375 ± 232 U/ml was used in the study. Serum KL-6 levels were well correlated with tumor progressiveness of lung cancer. KL-6 might be useful as a biological marker to predict acute exacerbation after resection for lung cancer. Methods: We retrospectively analyzes 97 patients with IP who had undergone pulmonary resection for lung cancer at Tokyo Medical and Dental University between July 2010 and December 2015. We examined sex, surgical procedures, serum markers of inflammation, bronchial obstruction, and the ratio of dPA to ascending aorta diameter (rPA) measured by CT are predictors of acute exacerbation after surgery. The predicted rate, and accuracy of rPA were 19.5%, 95.0%, 91.7%, and 35.2%, respectively. Conclusion: In interstitial pneumonia, rPA measured by CT is effective to predict acute exacerbation after pulmonary resection for lung cancer. Keywords: Interstitial pneumonia, pulmonary hypertension, pulmonary artery diameter.

P1.03-025 SERUM KL-6 LEVELS IN PATIENTS WITH LUNG CANCER
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Background: Serum levels of KL-6 are widely used as an indicator of activity of interstitial lung disease. Although KL-6 was initially developed as a serum marker for malignancies, it is still unknown if KL-6 can be used as a biological marker of lung cancer. The study aimed to determine the properties of serum KL-6 levels in patients with lung cancer. Methods: First, serum KL-6 levels were measured using non-linear least square analysis with the fitting equation: \( C(t) = C_0 \exp(-kt) + C_p \), where \( k \) is the rate constant of elimination. The biological half-life was calculated as \( \log(2)/k \). Next, serum KL-6, CEA, and CYFRA levels of patients with lung cancer and benign chest disease were retrospectively reviewed. A total of 226 patients with lung cancer and 103 patients with benign chest disease were included in this study. Serum KL-6 levels were measured using the electrochemiluminescence immunoassay method. The cut-off level of KL-6 was 500 U/ml. Results: Rate constant of elimination and biological half-life of KL-6 in initial 7 patients were 0.827 ± 0.275 day and 0.93 ± 0.35 day, respectively. These data implies that lung cancer cells produce KL-6 molecule and release it into the serum. Among 329 patients, serum KL-6 levels were above the cut-off level in 44 patients (19.5%) with lung cancer and 6 patients (3.9%) with benign chest disease. The mean serum KL-6 level in patients with lung cancer was significantly higher (375 ± 232 U/ml) than that in patients with benign chest disease (296 ± 177 U/ml). Serum KL-6 levels in patients with lung cancer were significantly correlated with tumor size (\( p < 0.0001 \)) and that was inferior to CEA (AUC=0.8127, \( p=0.0001 \)) and CYFRA (AUC=0.7103, \( p=0.0001 \)). The sensitivity, specificity, true positive rate, true negative rate, and accuracy of KL-6 were 19.5%, 95.0%, 91.7%, 35.2%, and 43.5%, respectively. Conclusion: Serum KL-6 levels are well correlated with the progressiveness of lung cancer. KL-6 might be useful as a biological marker to monitor the recurrence and the effect of therapy in lung cancer.

Keywords: tumor marker, KL-6

P1.03-026 MEASUREMENT OF PULMONARY ARTERY ON CT TO PREDICT ACUTE EXACERBATION OF INTERSTITIAL PNEUMONIA AFTER PULMONARY RESECTION FOR LUNG CANCER
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Background: Interstitial pneumonia (IP) is often accompanied by pulmonary hypertension (PH) that is considered to be fatal and has relation to acute exacerbation. To diagnost PH, right heart catheterization is generally required, but it is invasive. Nowadays pulmonary artery diameter is relatively easy to measure and the ratio of dPA to ascending aorta diameter (rPA) measured by CT are reported to be indicators of PH. We examined whether dPA and rPA could be predictors of acute exacerbation of IP after pulmonary resection for lung cancer. Methods: We retrospectively analyzes 97 patients with IP who had undergone pulmonary resection for lung cancer at Tokyo Medical and Dental University between July 2010 and December 2015. We examined sex, surgical procedures, serum markers of inflammation, bronchial obstruction, and the ratio of dPA to ascending aorta diameter (rPA) measured by CT are predictors of acute exacerbation after surgery. The predicted rate, and accuracy of rPA were 19.5%, 95.0%, 91.7%, and 35.2%, respectively. Conclusion: In interstitial pneumonia, rPA measured by CT is effective to predict acute exacerbation after pulmonary resection for lung cancer. Keywords: Interstitial pneumonia, pulmonary hypertension, pulmonary artery diameter.

P1.03-027 CLINICAL AND HISTOLOGICAL FEATURES ASSOCIATED WITH SUV IN FDG-PET-CT IN PATIENTS WITH ADENOCARCINOMA OF THE LUNG
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Background: FDG-PET-CT is increasingly used for staging and treatment monitoring in NSCLC. The prognostic and possibly predictive value of the standardized uptake-value (SUV), and the clinical, molecular and pathological features contributing to SUV levels have not been well described. Methods: We retrospectively reviewed the records of patients staged with FDG-PET-CT and correlated SUV values before and during treatment with clinical and pathological features of tumour including CRP as a marker of systemic inflammation, adenocarcinoma subtype (solid, lepidic etc.), and Ki67, as a marker of tumour proliferation. Results: 190 patients with adenocarcinoma of the lung were identified. 110 had FDG-PET-CT staging and were included in the analysis. Tumour subtypes were as follows: 50% solid, 16% papillary, 22% lepidic, 1.3% micropapillary, 15.4% other. 70 patients received systemic treatment and 40 were treated surgically. The mean primary-tumour-volume was 349 mL and the ratio of dPA to ascending aorta diameter (rPA) measured by CT are predictors of acute exacerbation after surgery. The predicted rate, and accuracy of rPA were 19.5%, 95.0%, 91.7%, 35.2%, and 43.5%, respectively. Conclusion: Serum KL-6 levels are well correlated with the progressiveness of lung cancer. KL-6 might be useful as a biological marker to monitor the recurrence and the effect of therapy in lung cancer.

Keywords: tumor marker, KL-6

P1.03-028 COMPUTATIONAL TEXTURE ASSESSMENT OF LUNG CANCER CT IMAGES IS HIGHLY ACCURATE IN PREDICTING ONSET OF ACUTE EXACERBATION AFTER PULMONARY RESECTION FOR LUNG CANCER
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Background: FDG-PET-CT is increasingly used for staging and treatment monitoring in NSCLC. The prognostic and possibly predictive value of the standardized uptake-value (SUV), and the clinical, molecular and pathological features contributing to SUV levels have not been well described. Methods: We retrospectively reviewed the records of patients staged with FDG-PET-CT and correlated SUV values before and during treatment with clinical and pathological features of tumour including CRP as a marker of systemic inflammation, adenocarcinoma subtype (solid, lepidic etc.), and Ki67, as a marker of tumour proliferation. Results: 190 patients with adenocarcinoma of the lung were identified. 110 had FDG-PET-CT staging and were included in the analysis. Tumour subtypes were as follows: 50% solid, 16% papillary, 22% lepidic, 1.3% micropapillary, 15.4% other. 70 patients received systemic treatment and 40 were treated surgically. The mean primary-tumour-volume was 349 mL and the ratio of dPA to ascending aorta diameter (rPA) measured by CT are predictors of acute exacerbation after surgery. The predicted rate, and accuracy of rPA were 19.5%, 95.0%, 91.7%, 35.2%, and 43.5%, respectively. Conclusion: Serum KL-6 levels are well correlated with the progressiveness of lung cancer. KL-6 might be useful as a biological marker to monitor the recurrence and the effect of therapy in lung cancer.

Keywords: tumor marker, KL-6

Figure 1. ROC curves showing performance of multivariate models comprising semantic (blue line), texture (red line), and combined (semantic and texture - green line) predictors. Conclusion: Combined semantic and computational texture assessment of lung cancer CT images is highly accurate in differentiation of SCCA and ADCA.

Keywords: non-small cell lung cancer, CT, Texture analysis, Diagnostic accuracy
Abstracts

Factors should be taken into account when interpreting FDG-PET-CT SUV values in clinical practice. The correlation of FDG-PET-CT SUV values with inflamed tumour phenotypes, and the possible predictive value of SUV for response to immune therapies, should be further investigated.

Keywords: PET-CT, Adenocarcinoma, proliferation, inflammation

P1.03-028 WOLF IN SHEEP’S CLOTHING - PRIMARY LUNG CANCER MIMICKING BENIGN DISEASES
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Background: Lung cancer is the biggest cancer killer and typically presents as mass or nodule, round or oval in shape. Restauration and diagnosis of these typical cases is often straightforward, whereas diagnosis of uncommon manifestations of primary lung cancer certainly is far more challenging. The aim of this pictorial essay is to illustrate the Computed Tomography (CT) and histopathology findings of uncommon manifestations of primary lung cancer with special focus on these entities that mimic benign diseases. Methods: Cases presented were collected during the Multidisciplinary Thoracic Oncology Tumor Board between January 2014 and May 2016 and have histopathologic proof. Results: Lung cancer can mimic a variety of benign diseases, including infection, granulomatous disease, lung abscess, postinfectious scarring, mediastinal mass and pleural disease. Previous history, clinical and biochemical parameters are certainly helpful and necessary in the assessment of these cases, but often aspecific and inconclusive. Whereas 18FDG-PET is the cornerstone in diagnosis and staging of lung cancer, it’s role in these uncommon manifestations is less straightforward since benign diseases, such as granulomatous and infectious diseases may also present with increased FDG-uptake. Chest CT is the imaging modality of choice and plays a central role in these cases. The usage of PET-CT in combination with correct clinical picture and correlation with other imaging modalities will be helpful for correct diagnosis.

Keywords: solitary pulmonary nodules, diagnosis, Multi-disciplinary team, logistic model

P1.03-029 A USEFUL ALGORITHMIC MODEL IN PREDICTING THE LIKELIHOOD OF LUNG CANCER IN SOLITARY PULMONARY NODULES
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Background: The aim of this study was to establish a mathematical model to predict the likelihood of lung cancer in surgically resected solitary pulmonary nodules (SPNs) and investigate the value of multidisciplinary treatment (MDT) consultation in diagnosis of SPNs. Methods: From January 2011 to June 2016, 666 patients with a clear pathological diagnosis of SPN by surgical resection in Fujian Provinical Cancer Hospital were involved. Their clinicopathologic data were collected and retrospectively analyzed. All patients were divided into testing and validating cohorts, testing cohort consisted of patients from January 2011 to June 2015, whose data were used to create a mathematical model via multivariate logistic regression analysis. Patients from July 2015 to June 2016 were included in validating cohort, whose data were used to verify the accuracy of the prediction model. The positive rate of malignancy between cases discussed at MDT meeting were compared with the positive rate of malignancy between cases not discussed at MDT meeting were evaluated by surgeon were compared. Results: The number of testing and validating cohort were 446 and 220, respectively. In testing cohort, there were 8 case (1.8%) diagnosed as atypical adenohyperplasia (AAH) and 313 cases (70.2%) as malignant SPNs, mainly invasive adenocarcinoma (IA, 234 cases/52.5%), small cell lung cancer (SCLC, 28 cases/6.3%), minimally invasive adenocarcinoma (MIA, 22 cases/4.9%) and adenocarcinoma in situ(AIS,10 cases/2.2%). Other were benign SPNs (125 cases, 28%), mainly including inflammation or fibrosis(95 cases, 21.3%), hamartoma (17 cases, 3.8%) and inflammatory pseudotumor (11 cases, 2.4%).Univariate analysis showed that there were significant differences between benign and malignant SPNs regarding age, sex, nodule type, maximum nodule diameter, CT value, nodule shape, spiculation, lobulation, pleural retraction sign, calcification, bronchole truncation and vascular convergence (P<0.05). Sex, age, nodule type, spiculation, vascular convergence, bronchole truncation and nodule shape were identified as independent predictors of malignancy in multivariate logistic regression analysis. The area under curve (AUC) was 0.883 (95% CI, 0.885-0.915) in the model. An appropriate cut-off point was determined as P=0.77, sensitivity and specificity of the model was 77.6% and 80.0%, respectively. The positive rate of malignancy in testing cohort was 81.3%(104/129) in cases discussed at MDT meeting, comparing with 72.0% in all patients(P<0.05). The positive rate of malignancy reach to 90.4% in 97 patients with model predicting positive and discussed by MDT. The validation data set is on-going. Conclusion: The prediction model established in this study could be useful in assessing the likelihood of lung cancer in SPNs. And MDT consultation can improve the accuracy of prediction.

Keywords: solitary pulmonary nodules, diagnosis, Multi-disciplinary team, logistic model

P1.03-030 FDG-PET/CT MIGHT BE A PREDICTOR FOR RESIDUAL DISEASE IN ADVANCED NSCLC AFTER CHEMORADIOThERApY
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Background: The standard treatment for locally advanced non-small-cell lung cancer (NSCLC) is chemoradiotherapy (CRT), some patients are considered for trimodality therapy represented by concurrent CRT followed by surgical resection. However, there is no validated clinical predictor for surgical resection after CRT. In the present study, we analyzed that the correlation between SUVmax of FDG-PET/CT in pre/post CRT and treatment effect. Methods: 22 patients with advanced NSCLC underwent CRT in Tokushima University Hospital between February 2006 to March 2016. We reviewed the medical records of 22 patients to obtain information on age, gender, histological type, clinical stage, adverse events, reduction ratio of tumor, SUVmax of FDG-PET/CT in pre/post CRT. Radiographic response was assessed by Modified Response Evaluation Criteria in Solid Tumors (RECIST) criteria. Toxicities were assessed according to the National Cancer Institute Common Toxicity Criteria (NCI-CTCAE). Results: Patient characteristics were as follows: average age of 65; male/female: 2/1; histologic type adenocarcinoma/squamous cell carcinoma/other: 14/5/3; clinical stage IIB/IIB/IIB/IIB/III/B: 5/3/1/1/1. Chemotherapy were platinum doubles regimen in almost cases. The average amounts of radiotherapy were 42.6Gy. The response rate was 29. The number of PR/SD were 10/22 in RECIST. The adverse events were following: G2/1(50%), G3/8(36%), G4,5/23(2%). 2cases stopped treatment because of adverse events. Operative procedure were followings: lobectomy/ bilobectomy/pneumonectomy: 17/2/3. The complication rate of operation was 27.2%, however, there was no hospital death. Overall survival was 69±10.3 months. Relapse free survival was 64.5±12.3 months. Pathological Complete Response(pCR) was recognized in 10cases(45.5%). The 4cases in 10cases of pCR got recurrence as distant metastasis, without local recurrence. The SUVmax decreasing rate was 69% in CRT. The SUVmax decreasing rate was 79% in the patients of pCR(n=5), however, this decreasing rate was 65% in not
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underwent CRT. The treatment response in local region was good in all cases. More than 70%. Conclusion: The pCR were recognized in 10/22 (45.5%) cases, on tumors with driver oncogene, including EGFR.

Background: Molecular targeted drugs are generally effective for metastasis.

In vivo imaging models for preclinical screening – Monday, December 5, 2016

P1.03-031 GYNECOLOGICAL MALIGNANCIES AND IMAGING PATTERNS. AN INTERESTING CASE REPORT AND LITERATURE SURVEILLANCE

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Background: Gynecologic malignancies are a heterogeneous group of common neoplasms in women. Thoracic abnormal findings exhibit various imaging patterns and are usually associated with locally invasive primary neoplasms or with intra-abdominal spread. It is not rare to find involvement occurring years post first diagnosis or as an isolated finding in patients without evidence of extra-abdominal neoplastic involvement. Thoracic metastases from gynecologic carcinomas typically manifest as pulmonary nodules and lymphadenopathy. Ovarian cancer often presents small pleural effusions and subtle pleural nodules whereas metastatic lung lesions, lymph nodes, pleura and pleural mesothelioma are thought to present calcification or mimicking granulomatous disease. Metastases from fallopian tube carcinomas have imaging features identical to ovarian cancers. Most cervical cancers are of squamous histology, and while solid pulmonary metastases are more common, the cavitary metastatic lesions occur more often. Metastatic chorionicarcinoma to lung characteristically exhibits solid pulmonary nodules. There are also reported pulmonary metastases from gynecologic malignancies with characteristic features such as cavitation (as awaited in squamous cell cervical cancer) and the “halo” sign (in hemorrhagic metastatic chorionicarcinoma lesions) and while computed tomography methods: When we report a case with a mass in left paratracheal area invading the lung hinting primary lung cancer. Results: The patient, female, 36 years old with previous medical history of resected cervical cancer, underwent endoscopy with aim to have transbronchial biopsy and while there was no histological evidence for malignancy the high SUV (12) uptake points at PET CT with intention to exclude lung cancer. She had the mass removed with all the surrounding lung parenchyma but unfortunately the final histologic report documented metastatic infiltration from cervical cancer in compliance with her previous medical history 6 years ago (in another hospital with radiotherapy only treated in adjuvant basis). She recovered well and was initiated chemotherapy for the gynecological malignancy She is now 2 years later alive with no residual disease. The basic is that malignancies are always suspected to be primary originated but the medical previous history should not be ignored, even the imaging tests tend to resemble to other entities. Conclusion: Therefore, radiologists should consider the presence of locoregional disease in combination with elevated tumor marker levels when interpreting imaging studies and all previous medical history of the patient’s malignancy to exclude metastatic disease.

Keywords: mass, gynecologic, imaging characteristics, cervical cancer

P1.03-032 IN VIVO IMAGING MODELS FOR PRECLINICAL SCREENING OF MOLECULAR TARGETED DRUGS AGAINST BRAIN METASTASIS

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Background: Molecular targeted drugs are generally effective on tumors with driver oncogene, including EGFR, ALK, and NTRK1. However, patients with these oncogenes frequently experience progression of brain metastasis during the targeted drug treatment. Thus, it is essential to establish more effective treatment for controlling brain metastasis. Methods: We established in vivo imaging brain tumor models by intracranial inoculation of human cancer cell lines, such as lung adenocarcinoma H1975 cells, the EGFR-L858R and T790M mutations, HGF-dependent gastric cancer NUGC4 cells, and TPM3-NTRK1 fusion gene positive colorectal cancer KM12SM cells, in SCID mice. We investigated the activity of several molecular targeted drugs on cell proliferation of these cell lines in vitro. In addition, we evaluated the efficacy of these drugs on brain tumor models, comparing with extracranial tumor models. Results: Results: In vitro condition, H1975 cells were sensitive to the 3rd generation EGFR inhibitor, osimertinib. HGF stimulated proliferation of gastric cancer NUGC4 cells, and the HGF-induced proliferation was inhibited by crizotinib, which has anti-MET activity, in a dose-dependent manner. KM12SM cells, which are the highly liver metastatic variant derived from TPM3-NTRK1 fusion gene positive colorectal cancer KM12 cells. KM12SM were sensitive to TRK-A inhibitors, crizotinib and entrectinib. In H1975-cell in vivo models, osimertinib (25mg/kg) inhibited the progression of both brain tumors and subcutaneous tumors. In NUGC4-cell in vivo models, crizotinib (50mg/kg) delayed the progression of brain tumors as well as peritoneal carcinomatosis, and prolonged the survival of the tumor bearing mice. In KM12SM-cell in vivo models, we evaluated the effect of crizotinib (50mg/kg) or entrectinib (15mg/kg) in the brain tumor model and liver metastasis model. Crizotinib treatment slightly delayed the progression of brain tumors but failed to prolong the survival of the recipient mice. Entrectinib treatment more discernibly delayed the progression of brain tumors and did prolong the survival. These results indicate that the effect of targeted drugs against brain tumors can be different from that against extracranial tumors. Conclusion: Conclusion: Our in vivo imaging brain tumor models may be useful for preclinical drug screening against brain metastasis.

Keywords: in vivo imaging models, Brain metastasis, drug screening

P1.03-033 ANALYSIS OF TO LUNG-RADS SCORES IN UI HEALTH’S MINORITY-BASED LUNG CANCER SCREENING PROGRAM AND COMPARISON TO THE NLST

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Background: Lung Cancer (LC) is the leading cause of cancer death in the U.S. The incidence and mortality differs depending on smoking status, race, ethnicity, gender, and socioeconomic status (SES). African Americans (AA) have significantly higher incidence/mortality rates of LC. The National Lung Screening Trial (NLST) which showed a 20% reduction in LC mortality with low-dose CT (LDCT) screening included 4.5% AA’s. LDCT screening amongst high risk minority individuals has not been sufficiently investigated. The goals of this study are: (1) to compare UI Health’s Screened Population (UIHSP) to the NLST and determine if NLST results are generalizable to an urban minority population; (2) to determine trends in UHSP Lung-RADS based on age, gender, race/ethnicity, smoking-history, and comorbidities. Methods: Patients were referred to LDCT based on U.S. Preventative Services Task Force guidelines. Summary statistics, such as means, standard deviations, and ranges for continuous variables, and frequencies for categorical variables are provided. Spearman correlation coefficients are estimated between continuous variables (i.e., age, smoking pack-years) and Lung-RADS scores are estimated. Chi-squared tests and Fisher’s Exact tests were performed to test the associations between categorical variables and Lung-RADS scores. All statistical tests are two-sided, controlling for a Type I error probability of 0.05. Results: Compared to the NLST, UIHSP has a higher percentage of AA’s (65% vs. 4.5%), rate of Lung-RADS 3 and 4 (30% vs 13.7%), UHSP had a LC rate 3x that of NLST on T0 scan (23% vs 7%). A diagnosis of emphysema on LDCT scans was significantly associated with higher Lung-RADS scores (p = 0.0045). Patients who were diagnosed with emphysema detected on LDCT report had significantly higher Lung-RADS scores. 5 LC diagnoses in the first 163 T0-scans (3%), 4 of 5 were AAs. Males were more likely to have Lung-RADS 3 and 4 than females (OR=2.1, p=0.0353). Smoking-pack years demonstrated a positive correlation with higher Lung-RADS score (p = 0.067). Conclusion: UIHSP compared to NLST demonstrated higher incidence of Lung-RADS 3 and 4 scores and diagnosis of LC at T0 LDCT scans. In addition this study has found a significant association between emphysema and higher Lung-RADS scores among UIHSP. These results support the conclusion from previous studies that emphysema on LDCT is an independent risk factor for LC. Furthermore, the
Posters

P1.03-034 IMPLEMENTING SMARTPHONE APPLICATION IN EARLY LUNG CANCER DETECTION AND SCREENING

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Background: The early detection of NSCLC is still a key point of the surgical treatment of lung cancer. Finding the symptomless patients requires the system of risk assessment, risk group selection and a controlled screening. The modern communication path of the mobile devices are enabling us a complete new communication and selection method which can effectively simplify the risk group identification and the suggestion of screening by the Screening Centers. The aim of our study was to determine the effectiveness of a lung cancer risk assessment mobile application (LungScreen) in a localised setting. Methods: A freely downloadable lung cancer risk assessment application (LungScreen) were created for Android and iOS mobile platforms. The application calculates and shows individual NSCLC risk based on Bach's protocol after collecting demographic data, smoking status, possible environmental harms of the participant. Based on GPS coordinates the high risk participant is navigated to the nearest Screening Center for further investigation. We analysed the records of the application in a test period of one year aided by an informative campaign in Hungary. Results: In one year test period more than 70000 participants downloaded and completed the risk assessment test (Male/Female 58%/42%, Age range 9-82 years, mean age 38,2 years). 16238 participants were active smokers, high risk criteria was calculated in 1831 cases, in which further screening investigation was suggested. In our region (Baranya County) 158 LDCT screening were performed, with 32 positive findings wich required further investigations. In 9 cases Tumor Board decided to indicated surgery (7 cases NSCLC, 2 cases benign lesion). All the procedures were performed with VATS. 6282 tests from other countries (e. g. Germany, France, UK, USA, Japan etc) Conclusion: Lung cancer risk assessment via mobile devices allows free, fast and efficient way to select, manage and localize high risk population for NSCLC. By omitting the complex recruitment process it can effectively fasten the screening trials and subsequently lower the financial needs. Giving immediate personalized feedback and individual direction to diagnostic centers can facilitate early diagnosis of operable NSCLC cases.

Keywords: smartphone application, lung cancer screening, Early Detection

P1.03-035 DOES SCREENING WITH LOW-DOSE COMPUTED TOMOGRAPHY (LDCT) OF ASBESTOS EXPOSED SUBJECTS REDUCE MORTALITY FOR LUNG CANCER (LC)?

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Background: Our previous prospective non-randomized ATOM002 study showed that LDCT screening of asbestos exposed subjects can identify LC at an earlier, and potentially more curable, stage than chest radiographs (CXR) (Fasola et al, The Oncologist 2007). The ATOM002 participants were selected from subjects enrolled in a surveillance program for asbestos exposed workers at the Monfalcone Occupational Health Unit in the Friuli Venezia Giulia (FVG) region, Italy. Here, we report a cohort mortality study of asbestos exposed subjects from that surveillance program, comparing outcomes in the ATOM002 participants and contemporary nonparticipants. Methods: Within a cohort of 2,423 asbestos exposed subjects, we compared mortality between the ATOM study participants (who had additional baseline and 1 year LDCT) and nonparticipants (n=926 and 1,507, respectively). The follow-up period spanned the years 2002-2011. Cox models were performed to assess survival for all causes, all cancers, LC and malignant pleural mesothelioma. Final models estimating mortality hazard ratios (HR) were adjusted for smoking habits, age, level of asbestos exposure and Charlson-Quan comorbidity index. For external comparison, we estimated the standardized mortality ratio rate (SMR) using FVG regional standard rates. Results: There was a significant 39.3% (95% CI: 3.9-82.8) reduction in adjusted mortality for LC among ATOM002 participants vs. nonparticipants. LC crude mortality was 39.4 per 100,000 person-year in participants (8 LC deaths) compared to 430.4 per 100,000 person-year in nonparticipants (50 LC deaths). Mortality was also reduced for all causes (HR=0.61; 95% CI: 0.44-0.84), but not for all cancers (HR=0.97; 95% CI: 0.62-1.50) or malignant pleural mesothelioma (HR=0.86; 95% CI: 0.31-2.41). Compared with regional mortality rates, a trend towards reduced mortality for LC was found among ATOM002 participants (SMR=0.55; 95% CI: 0.24-1.09), in contrast to a statistically significant increase in the nonparticipants (SMR = 2.07; 95% CI: 1.53-2.73). Conclusion: In our cohort, participation in the LDCT based screening study was associated with reduced mortality for LC compared to empirc CXR based public health surveillance. To our knowledge, this is the first report suggesting reduction in mortality for LC with LDCT screening in an asbestos exposed population. LDCT screening might therefore be a reasonable approach for surveillance in these populations.

Keywords: asbestos, Screening, lung cancer, low-dose computed tomography

P1.03-036 ADHERENCE TO ELIGIBILITY CRITERIA FOR LOW-DOSE CT SCREENING IN AN ACADEMIC CENTER

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Background: The United States Preventive Services Task Force (USPSTF), Centers for Medicare and Medicaid Services (CMS), and the National Comprehensive Cancer Network (NCCN) recommend low dose computed tomography (LDCT) lung cancer screening for high risk patients, defined as those between age 55-77 (CMS) or 55-80 (USPSTF), with ≥30 pack-year smoking history who currently smoke or quit within the past 15 years. The USPSTF guidelines also recommend screening for patients over 50 years with ≥20 pack-year smoking history and at least one additional lung cancer risk factor. To better understand community practices, we describe adherence to screening eligibility criteria for the population screened at the Seattle Cancer Care Alliance (SCCA). Methods: The SCCA developed a multidisciplinary LDCT screening program that executes LDCT screening orders when patients' regional primary care providers deem them eligible for screening, and provides follow-up evaluations based on screening results. From a prospective registry study of patients screened at the SCCA, we collected baseline sociodemographic, smoking history, and clinical data to retroactively assess patients' screening eligibility based on USPSTF, CMS, and NCCN screening criteria, respectively. Seventy-nine (75%) patients met eligibility criteria for at least one guideline. Of the 27 patients ineligible by any guideline, 17 (63%) had ≥20 pack-year smoking history and 5 (19%) were under age 50. White patients were more likely to be eligible for at least one guideline (Odds Ratio= 7.3; 95% CI 1.9-27.8). Conclusion: In this single-center registry study, 25% of patients did not meet screening eligibility criteria when primary care providers were responsible for identifying screening candidates. In response to these results, the program employed a coordinator to pro-actively review screening orders to confirm guideline compliance. An opportunity exists to prioritize LDCT screening to high risk patients through patient counseling, provider education and pro-active review of screening CT orders.

Keywords: screening eligibility, screening guidelines, Low-Dose Computed Tomography (LDCT)
Background: Screening programs increased identification of small or indistinct pulmonary lesions which are difficult to localize. We report our experience in their preoperative localization by radiotracer and resection. Methods: Patients with pulmonary nodule of subsolid morphology or smaller than 1 cm and/or deeper 1 cm below the visceral pleura underwent computer-tomography (CT)-guided injection of radiotracer technetium99m macroaggregates in vicinity of the lesion. During surgery, a handheld gamma probe was used to detect hot spot where radioactive was localized and this area was resected. Results: From November 2007 to December 2013, 112 patients (58 men; median age 62 years) underwent preoperative radiotracer injection with a successful marking in all patients. Complications included 33 pneumothoraces (29.4%) (one requiring chest tube placement), 23 (20.5%) parenchymal hemorrhage softfusions, and 1 (0.9%) allergic reaction to contrast medium. In all cases, except for 2, gamma probe revealed pulmonary lesion. Overall, 123 pulmonary nodules were localized and resected. Mean distance from the pleura was 12 mm (range, 0 to 39 mm), Pulmonary resection was performed by thoracoscopic in 70 (62.5%) cases, thoracotomy in 36 (32.1%), and converted thoracoscopic to thoracotomy in 6 (5.4%). Mean nodule size was 9 mm (range, 3-24 mm). Histology showed 14 (11.4%) benign lesions and 109 (88.6%) malignant lesions (85 primary lung cancers, and 24 metastases). Conclusion: Radiotracer localization of pulmonary lesions is a simple and feasible procedure with a high rate of success. Optimal candidates are patients with suspicious nodules detected by screening or incidental CT due to high rate of nonsolid morphology and small size.

Keywords: radiology, lung tumor, Surgery
Background: The National Lung Cancer Screening Trial has shown that lung cancer screening (LCS) with an annual low-dose chest CT-scan reduces specific mortality in both former and current heavy smokers. However, organizational issues have yet to be solved before it can be systematically implemented. We investigated the perceptions of the population at large as well as those of physicians with regard to the efficacy of LCS, and target populations in terms of tobacco-use. Methods: The 4th French nationwide observational survey, EDIFIC4, was conducted by phone interviews of a representative sample of 1602 subjects, aged between 40 and 75 years, from June 12 to July 10, 2014. A mirror survey was also conducted by phone among physicians between July 9 and August 8, 2014. Both surveys were conducted using the question method on representative samples of 1463 lay persons and 301 physicians with no history of cancer. Results: For 53% of lay persons and 33% of physicians interviewed (P<0.01), generalization of LCS is potentially an effective way to reduce lung cancer mortality. For the majority of interviewees (58% of lay persons and 55% of physicians), there is no statistical test (P<0.05) for LCS to the whole population would not encourage smokers to continue smoking. The table shows lay persons’ and physicians’ replies concerning target populations within the whole population and among smokers.

Keywords: Lay persons, physicians, target population

## P1.03-042 NODULE SIZE IS POORLY REPRESENTED BY NODULE DIAMETER IN LOW-DOSE CT LUNG CANCER SCREENING

### Background

In lung cancer screening, at least one pulmonary nodule is found in over 50% of participants, of which 9% is benign. As lung cancer probability in low-dose computed tomography (CT) lung cancer screening usually is based on nodule size and growth rate, accurate nodule size determination is of major importance to decrease false positive screen results. Previous studies showed that nodule size measurements based on semi-automated volume are preferred over diameter measurements. Aim of this study was to determine the correlation between nodule diameter and nodule size of nodules found in low-dose CT lung cancer screening, and to directly compare it with semi-automated volume measurements. Methods: We investigated baseline data of 2,420 solid nodules of intermediate size (volume 50-500 mm³) in 1,500 lung cancer screening participants. Nodule volume, x, y, and z diameter and minimum / maximum diameter in any direction were generated by semi-automated software (LungCare, Siemens). Range in maximum axial and mean nodule diameter per nodule volume category (50-100 mm³, 100-200 mm³, 200-300 mm³, 300-400 mm³, 400-500 mm³) was determined. Semi-automated nodule volume represented nodule size. Intra-nodule diameter variation was defined as maximum minus minimum nodule diameter. Results: Median participant age was 59 years, 14% were women. Median nodule volume was 224.6 mm³ (interquartile range [IQR]; 62.9–125.4 mm³). Median nodule diameter was 6.1 mm (IQR; 5.4–7.2 mm) for mean diameter, and 6.6 mm (IQR; 5.9–7.7 mm) for maximum axial diameter. Range in mean nodule diameter per volume category varied from 8.55 mm (3.0 – 11.5 mm) for nodules with volume of 50-100 mm³ to 6.1 mm (7.2 – 13.3 mm) for nodules with volume of 200-300 mm³; range in maximum axial diameter varied from 11.2 mm (7.3 – 13.5 mm) for nodules with volume of 200-300 mm³ to 7.0 mm (9.1 – 16.1 mm) for nodules with volume of 400-500 mm³. Intra-nodule diameters varied by a median of 2.8 mm (IQR; 2.2-3.7 mm). Intra-nodule diameter variation for smaller intermediate-sized nodules (50-200 mm³) was 2.8 mm (IQR 2.2–3.5 mm), and was smaller than intra-nodule diameter variation for larger intermediate-sized nodules (200-500 mm³); median 3.6 mm (IQR 2.5-5.1 mm), P<0.01). Conclusion: Nodule size is poorly represented by diameter, as a nodule has an infinite number of diameters, but only one volume. Therefore, use of nodule diameter measurements may lead to misclassification of lung cancer probability. Median intra-nodule diameter variation was found to be higher as the 1.5mm LungRADS cutoff for nodule growth.

Keywords: pulmonary nodule, computed tomography, Screening

## P1.03-041 DO SEVERAL ROUNDS OF NEGATIVE SCREENING LOW DOSE CT SCANS INFLUENCE THE RISK TO DEVELOP LUNG CANCER?

### Background

The purpose of this study was to assess whether several years of negative screening low-dose computed tomography (LDCT) scans predict a subsequent lower risk of developing lung cancer. This would have implications for recommended intervals and duration of LDCT lung cancer screening. Methods: The cohort was an at-risk population who had previous negative screening LDCTs and had not been screened for at least 5 years. Between 2003 and 2009, 4782 individuals had been enrolled in a lung cancer screening study based on age and smoking alone. At this time, their risk was re-calculated using a multifactorial assessment model, and they were contacted in decreasing order of their re-calculated risk. An initial phone interview assessed interim history, general health, interim diagnosis of lung cancer or interim chest CT. Those participants without lung cancer or recent CT were invited for a single LDCT (40mA, 135kV, 1mm axial reconstructions). Subsequent investigation was recommended depending on the LDCT findings: negative, no new or growing nodules (no further recommendation), positive, low suspicion for malignancy (follow up CT in 3-6 months) or positive, high suspicion for malignancy (referral to the local lung cancer rapid diagnostic assessment program). Results: To date, 361 individuals or family members have been contacted. Fifty-five individuals had passed away (20 from lung cancer), 24 were alive with lung cancer. 129 did not qualify for a LDCT scan (declined participation, or recent CT). A total of 153 have attended for LDCT, on average 7 years after their last LDCT. Ninety-one (59%) studies were reported as negative. Forty-five (29%) LDCTs were positive with low suspicion and a follow up scan was recommended; 13 cases nodules had resolved on follow up imaging, the remaining 32 are awaiting surveillances LDCTs. Seventeen (11%) LDCTs were reported as positive with high suspicion; 11 of those have a subsequently biopsy proven lung cancer and 6 are currently undergoing further investigations or LDCT surveillances. All lung cancers diagnosed were either stage I or II. Of the 11 individuals with biopsy proven cancers, 7 had normal previous CTs, 4 had a pre-existing groundglass nodules in the tumor location on the most recent exam. The overall prevalence of lung cancer in this cohort is 15.2% (55/361) and it may increase. The detection rate of LDCT to date is 7.2% (11/153). Conclusion: Lung cancer risk remains high despite several negative annual screening LDCT scans. Continued screening beyond three years is recommended in high risk individuals.

Keywords: Low dose computed tomography, lung cancer, Screening

## P1.03-043 PRACTICAL DIVERSITY OF LOW DOSE COMPUTERIZED TOMOGRAPHY AS A LUNG CANCER SCREENING TOOL IN AN ENDOemic AREA OF TUBERCULOSIS

### Background

Low-dose computerized tomography (LDCT) is a current standard technique for lung cancer screening to reduce lung cancer death. Clinical and radiographic finding for lung cancer can also be found in tuberculosis (TB). No clear evidence of benefits from lung cancer screening has been established in a high-risk population residing in an endemic area of TB. Methods: A 5-year prospective lung cancer screening using LDCT enrolled 634 former or current heavy smokers (50 pack-year aged 50-70 years without a...
of positive LDCT test, NCN(s)>10 mm and GGN(s)>10 mm for diagnosis lung stage II/III, 22% stage IV) within 12 months. All cases of stage I-II had 2-10 obstructive atelectasis, pleural effusion, or mediastinal lymphadenopathy). Most of participants with non calcified lung nodule(NCN(s)) had 2-4 nodules, the higher proportion of multiple pulmonary nodules was observed in larger size. Nine cases (1.4%) were proven lung cancer (56% stage I, 22% stage II/III, 22% stage IV) within 12 months. All cases of stage I-II had 2-10 lung nodules, while all stage III-IV lung cancers had single lung nodule. PPV of positive LDCT test, NCN(s)/10 mm and GGN(s)/10 mm for diagnosis lung cancer were 27.3%, 40%, and 75%, respectively. The incidence of lung cancer in T1 and T2 were 0.67% and 0.70%, respectively. Half of them had baseline lesions suspected inflammation/infection. The incidence of active pulmonary TB in T1 and T2 was 0.50% and 0.52%, respectively. Conclusion: Despite a high burden of TB in Thailand, LDCT screening in heavy smokers could yield a high rate of early stage of primary lung cancer in this population at risk and also high rate of active pulmonary tuberculosis. However, high prevalence of lung nodules and high proportion of multiple pulmonary nodules of individuals were major problems in diagnosis and staging lung cancer in endemic area of Tuberculosis. Regarding the high probability of malignancy in GGN diameter >10 mm and newly seen or progressive lesion of baseline lesion suspected of inflammation/infection, nodule management protocol would be adapted in this population.

Keywords: lung cancer screening, low dose CT, Pulmonary Tuberculosis

Background: Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS–TBNA) was introduced to provide access to mediastinal and hilar lymph nodes. However, it is difficult to EBUS to approach the aorto-pulmonary window and paraseptal hilar stations. Transesophageal endoscopic ultrasound-guided EUS (EUS-FA) was introduced to provide access to this area. In addition, transgastrroduodenal endoscopic ultrasound can evaluate abdominal lesions. Methods: Endoscopic ultrasound fine needle aspiration (EUS-FNA) was performed under conscious sedation with the administration of intravenous midazolam and pethidine hydrochloride. It was performed with a convex array echoendoscope connected to an ultrasound scanning system. Lymph nodes of paraseptal, subcarinal, lower paratracheal, subaortic, and upper paratracheal regions were evaluated from esophagus. Left adrenal gland and right adrenal gland were evaluated from stomach and duodenum. After obtaining tissue via EUS-FNA, the tissue was reviewed immediately (rapid on-site cytopathological evaluation: ROSE) by a cytopathologist. Subsequent punctures in the same patient were not performed before confirming the results of ROSE so as to minimize the complications. Results: As to the lymph node level, the lower mediastinal and the aorto-pulmonary window were parts for detection by transesophageal EUS, whereas pretracheal and hilar lymph nodes are out of reach because of the interference of air from the trachea and bronchi. EUS was chosen to assess the posterior mediastinum nodes (R5, 7, 8, 9) but not the anterior ones. A final diagnosis was obtained by EUS-FNA in 76 patients. The lesions sampled were mediastinal cancers in total. Early EUS-Lung was negative in the two small cell cancers. There are 58 Early EUS-Lung biomarker positive individuals with a LDCT without nodules. (NCT017000257) Conclusion: The Early EUS-Lung biomarker was more likely to be positive in patients with nodules and lung cancer cases, particularly early stage lung cancer. Accrual to the study and follow-up of 38 biomarker positive but LDCT negative participants continues.

Keywords: Screening, LDCT, auto-antibodies

Background: The Early Cancer Detection Test (CDT)-Lung is a serum-based biomarker consisting of a panel of tumor-associated autoantibodies that has been shown to detect lung cancer. We hypothesized that this biomarker when used in combination with a low-dose CT (LDCT) in screening of an at-risk population would increase the detection of early stage lung cancer. Methods: A prospective study of 1,600 subjects at high risk for lung cancer was designed. Eligibility criteria included persons 50-75 years of age, current or former smokers of ≥20 pack years and <10 years since quit smoking. Those with a history of lung cancer in first-degree relative(s) and any history of smoking were included. Exclusion criteria were any history of cancer within 10 years (except skin cancer), any use of oxygen, and life expectancy of ≤5 years. Those fitting inclusion criteria received the Early CDT-Lung blood test and a LDCT. A nodule of ≥3mm was considered as a positive scan. The Early CDT-Lung test was considered positive if any one of the seven autoantibodies was positive. Telephone follow-up was conducted over two years. Results: From May 2012 through June 2016, 1235 individuals were enrolled. The cohort median age was 59 years with 55% female and 45% male gender distribution. Fifty-two per cent were current smokers while 48% were former smokers. Seventy-one per cent of the LDCTs were negative for any lung nodule while 29% were positive. The Early CDT-Lung biomarker was positive in 88% (7%) of participants. In those with a positive LDCT (n=352), the biomarker was positive in 30 (8.5%). As of June 30, 2015, there have been seven confirmed lung cancers: two limited stage small cell, two stage IB adenocarcinoma (ACA), and three stage IA (two ACA and one squamous cell). The Early CDT-Lung blood test was positive in 2 of the 7 (29%) total cancers, both stage IA. Early CDT-Lung was positive in 2 of 5 (40%) Stage IA/IB lung cancers in total. Early CDT-Lung was negative in the two small cell cancers. There are 58 Early CDT-Lung biomarker positive individuals with a LDCT without nodules. (NCT017000257) Conclusion: The Early CDT-Lung biomarker was more likely to be positive in patients with nodules and lung cancer cases, particularly early stage lung cancer. Accrual to the study and follow-up of 38 biomarker positive but LDCT negative participants continues.

Keywords: Screening, LDCT, auto-antibodies

Background: Low Dose Computer Tomography (LDCT) screening has been shown effective in reducing overall and lung cancer mortality, but there are still concerns for efficiency and the cost/harm benefit ratio. reduce costs. Subjects enrolled in trials evaluating LDCT as a test for the early detection of lung cancer represent the population in which to study the possible use of molecular markers in a combined approach of screening. Methods: Out of 1406 subjects randomised in the intervention arm of the ITALUNG study and attending at baseline test, 1356 were enrolled, after specific consent, in the ITALUNG biomarker study. Screen detected lung cancers detected over the 4-years of screening included out of 38 in ITALUNG active arm of 845 randomly selected subjects without lung cancer at end of the study follow-up, were included in this analysis. DNA in plasma was quantified at baseline by Real Time PCR; microsatellite instability (MSI) and loss of heterozygosity (LOH) was assessed in blood and sputum. ITALUNG Biomarker Panel (IBP) was

Keywords: biopsy, lymph node, EUS, Genetic analysis
considered as positive if MSI/LH or DNA Pool values (cutoff 5% / ml) were positive. Results: The IBP results are shown in Table 1. Accuracy measure were estimated and showed high sensitivity for baseline screen-detected cases (84.4%) with a specificity of 60.0% (ROC Area 77%). Sensitivity and specificity were 65.7% and 60.1% for lung cancers screen-detected at repeated LDCT (ROC Area 63.4%).

Table 1

| Biological | Baseline | Lung cancer at | Baseline | Lung cancer at | Biological |
| specimen, and molecular test | negative at baseline screening | repeated | negative at baseline screening | repeated | negative at baseline screening |
| N = 235 | N = 118 | N = 10 | N = 18 | N = 18 |
| IBP positive | 97 | 97 | 48 | 17 | 12 |
| (41.3%) | (39.8%) | (37.5%) | (94.4%) | (66.7%) |
| *NCN = Non Calcified Nodule < 5mm at baseline and < 3mm at repeated test |

Conclusion: The IBP showed good accuracy for the identification of screen detected baseline lung cancers, with a very high sensitivity and a specificity of about 60%. The analysis of IBP of the baseline sample showed low prediction at repeated test. IBP was confirmed as a potentially valid tool for baseline selection of high-risk subjects, saving about the 60% of the tests. Low predictive capacity of screen detected cases at repeated tests needs further investigation.

Keywords: high-risk, lung cancer, Screening, biomarker

Poster Session 1 P1.03: Radiology/Staging/Screening

P1.03-048 A STRUCTURED LUNG CANCER SCREENING PROGRAM FACILITATES PATIENT AND PROVIDER COMPLIANCE

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Background: In the United States, both private insurers and Medicare provide coverage for low-dose computed tomography (LDCT) screening for lung cancer. Medicare has defined specific criteria for coverage to include “lung cancer screening counseling and shared decision making visit”. Currently, many institutions follow the same guidelines for LDCT screening. However, it is possible for Medicare eligibility to be performed without documentation of these discussions. We hypothesize that performing LDCT screening in the context of a structured lung cancer screening program results in improved compliance with coverage regulations. Methods: Medical records of patients undergoing LDCT screening at our institution between January 1, 2015 and June 30, 2016 were reviewed. Chart abstraction included eligibility criteria and documentation of shared decision making, discussion of adherence to annual screening and discussion of tobacco cessation/continued abstinence. Results: Of the 597 patients who had LDCT screening in the defined time period, 223 (37.7%) were seen in the Lung Cancer Screening Clinic and 368 (62.3%) had studies ordered by other providers. Within the Lung Cancer Screening Clinic (LCSC) cohort, 202/223 (90.6%) met Medicare eligibility and 17/223 (7.6%) met National Comprehensive Cancer Network (NCCN) “Category 2” criteria for lung cancer screening. In the “other provider” (OP) cohort, 281 (76.4%) met Medicare eligibility and 24 (6.5%) met NCCN “Category 2” criteria for screening (p<0.0001). Current smokers were more likely to have documented discussion of tobacco cessation counseling (99.2% vs. 62.0%, respectively; p<0.0001). Similarly, patients seen in the LCSC were more likely to have documentation of shared decision making than those in the OP cohort (97.3% vs. 93.3%, respectively; p<0.0001).

Keywords: lung cancer screening, low-dose CT

Poster Session 1 P1.03: Radiology/Staging/Screening

P1.03-047 COMMUNITY-BASED LOW-DOSE COMPUTED TOMOGRAPHY (LDCT) LUNG CANCER SCREENING IN THE US HISTOPLOSOMOSIS BELT: ONE YEAR FOLLOWUP

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Background: LDCT lung cancer screening has been incorporated into most major American medical societies’ screening guidelines. However, its performance in a non-tertiary care community setting with a high prevalence of fungal infections has not been sufficiently studied. Methods: Beginning in April 2013, high-risk adults ages 55-80 with at least a 30-pack-year smoking history, including former smokers who had quit within the previous 15 years, were prospectively evaluated with an LDCT scan performed at our community hospital. Results: As of June 2016, we present data on 466 evaluable participants (compared to 176 from one year ago), 234 of whom were men (50%). The median age of the studied population remains 64 years (range 55-80). Screening adherence has dropped from 97% to 91%, with 40 participants lost to follow-up. 27 participants have completed all required phases of the screening, 192 participants (64%) had positive baseline screening tests. 26 of those participants (6% of the total population) required further evaluation with PET scans. 15 of these PET scans were performed by invasive procedures, including lung biopsy. 13 biopsy-proven malignancies (3%) were detected as a direct result of the screening. 12 malignancies were NSCLCs, of which 9 were early-stage (stages I-II). The thirteenth malignancy, a stage I Marginal Zone Non-Hodgkin Lymphoma of the lung, was confirmed by a lung wedge biopsy. Of the other two participants requiring invasive diagnostic procedure, one had a biopsy “negative for malignancy” and the other was diagnosed with histoplasmosis. No biopsy-related complications occurred. Twelve of thirteen participants with biopsy-proven malignancies are still alive and doing well. One participant died secondary to an advanced NSCLC detected by the screening program. Conclusion: This report represents an update on, to our knowledge, the first community hospital-based study evaluating the results of LDCT lung cancer screening in an area of the United States endemic for both histoplasmosis and blastomycosis. Only one case of histoplasmosis has been confirmed by invasive diagnostic procedure. A significant number of early stage lung cancers were detected without excessive testing or complications.

Keywords: lung cancer, histoplasmosis, Screening, community
Background: Patients within the National Lung Screening Trial (NLST) undergoing low-dose computed tomography (LDCT) lung cancer screening (LCS) with abnormal results were more likely to quit smoking (Tammemagi et al.). However, these results may not be generalizable to underserved, ethnic minorities. Despite high incidence and mortality of smoking-related lung cancer among African Americans (AAs), few efficacy smoking cessation trials in LCS participants have included AAs. The National Lung Screening Trial-Lung Cancer Screening (LCS) with abnormal results were more likely to quit smoking (Tammemagi et al.). Thus, we studied smoking patterns in a predominantly AA population undergoing lung cancer screening. Methods: In a predominantly AA population we studied those undergoing LDCT-LCS (n=116). These patients received shared decision making, LDCT-LCS, results and smoking cessation in a single visit. Patients self-reported smoking status six months following LDCT. Results: Of 116 patients receiving lung cancer screening, 100 (86%) were AAs, 30 (21%) Caucasians, 14 (10%) Hispanics and 2 (1%) Asians. Smoking history was a mean of 49 pack years, median of 62 pack years with 60% current smokers. Of the 88 active smokers, 86 received greater than 10 minutes of smoking cessation counseling, 61 received a prescription for smoking cessation medications, and 60 agreed to follow up smoking cessation appointments. The overall quit rate was 11% (10 out of 88 active smokers). Quit rate for smokers who declined medical assistance was 4% (1 out of 28). Smokers who also agreed to follow up visits in addition to receiving a personalized combination of smoking cessation medications had a quit rate of 33% (5 out of 15). Quit rate was 20% for people with normal LDCT, Lung-RADS category 1 (8 out of 40) and 5% for people with benign appearing nodules, Lung-RADS category 2 (2 out of 4). None of the 3 people with nodules requiring further follow up, Lung-RADS category 3, or 6 people with nodules suspicious for cancer Lung-RADS category 4, quit smoking within 6 months of their LDCT conclusion. In a predominantly AA population, 60% of screened LDCT-LCS were active smokers, only 11% quit despite a rigorous smoking cessation program. Different from the NLST population, our findings indicate that patients without suspicious nodules were more likely to quit than those with suspicious nodules. The causes of these differing results are unknown. We theorize that the differences may be due to biological, cultural, psychological and socioeconomic factors. We suggest that future research should aim to examine these factors to identify barriers and facilitators to changing smoking behaviors among those undergoing LDCT-LCS.

Keywords: delivery of health care, Disparity of health care, lung cancer screening, Smoking Cessation

P1.03-050 OUTCOMES AFTER THE DECISION TO BIOPSY: RESULTS FROM A NURSE PRACTITIONER RUN MULTIDISCIPLINARY LUNG CANCER SCREENING PROGRAM

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Background: Lung cancer screening programs are increasing in popularity after results from the National Lung Screening Trial demonstrated improved mortality after screening with low-dose computed tomography. Current guidelines recommend the availability of multidisciplinary care and evaluation; however, reported outcomes from multidisciplinary team decision making to proceed with diagnostic sampling in lung cancer screening remains sparse. Methods: A retrospective review of patients enrolled in the Swedish Cancer Institute Lung Cancer Screening Program from January 2013 to March 2016 was performed. The program is run by an independently practicing nurse practitioner, with a multidisciplinary team consisting of radiologists, interventional pulmonologists, and thoracic surgeons. Positive screening results (nodules ≥3mm) with the potential need to pursue diagnostic sampling were reviewed in a multidisciplinary fashion. Basic demographics and procedural outcomes after the decision to biopsy were obtained. Results: A total of 516 patients were enrolled within the lung cancer screening program from 2013 – 2016. Nodule(s) ≥3mm were identified in 516 patients (31%). Subsequently, 25 patients underwent a form of invasive testing. The mean age of this population was 66.2 (SD 6.7) years with 56% (14/25) being female and mean pack years of 50.8 (SD 19.5).

P1.03-051 MEDICALLY UNDERSERVED AND GEOGRAPHICALLY REMOTE INDIVIDUALS MAY BE UNDERREPRESENTED IN CURRENT LUNG CANCER SCREENING PROGRAMS

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Background: The National Lung Screening Trial demonstrated a 20% reduction in lung cancer mortality and ushered in lung cancer screening (LCS). Study centers included 33 academic, mostly urban-based sites, which may underrepresent low socioeconomic remote populations with minimal health care access. United States Census Bureau data demonstrated that smoking is concentrated among adults with low income and education, and without private medical insurance; components of medically underserved/shortage area designations. We sought to assess the representation of underserved communities in our hospital-based Lung Cancer Screening Program (LCSP). Methods: We reviewed individuals referred to our LCSP from 2012-2016, consisting of two separate screening sites located within metropolitan King County, Washington. Each individual’s county and distance from the LCS site was calculated. Individual’s residence designation as a geographic medically underserved defined shortage area was determined. Definitions include: medically underserved area (MUA, healthcare resources deficient region), medically underserved population (MUP, area with economic/cultural/linguistic barriers to primary care services), health professional shortage area (HPSA; primary care physician shortage). Results: We identified 599 referred individuals, median age 64, from 33/39 counties (King County and 12 clustered, surrounding counties). Overall, 20% of the referred population resided in underserved/shortage areas and ≤5% of the designated geographic underserved/shortage areas in the 13 counties had patient referrals (Table). Of those referred, 85% resided in King County, 17% in a MUA and 65% of the MUs had patient referrals. Two percent of the referred population resided in a remote county, Clallam, where ≥20% of referred households were in underserved/shortage areas.
Abstracts

Conclusion: The majority of individuals referred reside within 10 miles of the LCS site. Less than 20% reside in designated underserved/shortage areas and ≤5% of underserved/shortage areas are represented. Creative and coordinated approaches, like Telemedicine, will be required to address the potential lack of LCS services in underserved/shortage areas and facilitate individuals remaining in their communities.

Keywords: lung cancer screening, medically underserved area/population, Health professional shortage area, Geographically remote

POSTER SESSION 1 - P1.03: RADIOLOGY/StAGING/SCREENING

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P1.03-052 THE EFFECT OF ROUNDING ON RATE OF POSITIVE RESULTS ON CT SCREENING FOR LUNG CANCER

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Background: Effective management of small pulmonary nodules to reduce frequency of false positives has been one of the most challenging issues to implementation of screening. Measurement of size is important as it determines whether a nodule is positive result and also whether growth has occurred. Lung-RADS v1 guideline requires nodule measurement to be rounded to the nearest whole number, it is not specified whether individual length and width measures should also be rounded prior to rounding the diameter. An alternative approach is the one used in I-ELCAP where measurements were recorded to one decimal place. This study explored how rounding would affect the frequency of positive results both for baseline and annual rounds. Methods: Using data collected from CT screenings of 21,136 I-ELCAP participants, we evaluated four different approaches for calculating the nodule diameter (D) based on measurements of the long axis (L) and width (W) listed below: 1) Measurement of L and W to one decimal place (x.x) and calculation of D without rounding; 2) rounding D to the nearest integer; 3) rounding the L and W measurements to the nearest integer before calculating D with no further rounding; and 4) rounding the calculated D determined by method 3 to the nearest integer. Threshold of positive results was 6.0 mm for baseline round and 4.0 mm for annual repeat rounds of screening. Frequency of positive results in the baseline and annual repeat rounds were compared. Results: For baseline screening using the current I-ELCAP definition (Method 1), the rate of positive results was 10.2%. Using method 2, 3 and 4, positive rates were 12.8%, 10.5% and 13.2%, respectively. Use of rounding would have increased the frequency of positive results by 25.7%, 3.0%, and 28.9%, respectively. Of 85,877 repeat screenings, the rate of positive results was 8.0% using method 1. Using method 2, 3, and 4, positive rates were 9.7%, 8.3% and 9.8%, respectively. Use of rounding would have increased the frequency of positive results on repeat screenings by 20.2%, 3.2% and 22.9%, respectively. Conclusion: Regardless of where the rounding occurred, it results in more nodules designated as positive. This effect is most pronounced when the rounding occurs in average diameter, and since frequency of nodules increases as size decreases, small nodules are therefore the most frequent cause for positive results and rounding can lead to large increases in positive rates.

Keywords: CT screening, nodule measurement, positive results, rounding numbers

POSTER SESSION 1 - P1.03: RADIOLOGY/StAGING/SCREENING

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P1.03-053 THE EFFECT OF PRIMARY CARE PHYSICIAN KNOWLEDGE OF LUNG CANCER SCREENING GUIDELINES ON PERCEPTIONS AND UTILIZATION OF LOW DOSE CT

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Background: Lung cancer screening with low-dose computed tomography (LDCT) is recommended by the U.S. Preventive Services Task Force (USPSTF) in high-risk patients, but a minority of eligible people is screened. It is unknown whether knowledge of USPSTF recommendations among primary care physicians (PCP) impacts perceived benefits and utilization of LDCT.

Methods: As we previously reported, a randomly selected sample of 1384 primary care physicians in Los Angeles County was surveyed between January and October 2015, using surveys sent by mail, fax, and email. The response rate was 18%. Training background, years in practice, practice location, and respondent demographics were collected. We analyzed results based on the response to a question on whether the USPSTF recommends the use of LDCT to screen high-risk individuals for lung cancer. Results: One hundred seventeen (47%) PCPs responded that the USPSTF recommends LDCT for LCS. Of PCPs who were aware of USPSTF recommendations, 94% responded that CT was somewhat or very effective at reducing lung cancer mortality among individuals meeting eligibility criteria, compared with 79% who were unaware (p=0.013). 27% of those aware of the recommendations thought chest x-ray (CXR) was effective at reducing lung cancer mortality compared with 62% of unaware PCPs (p=0.001). A similar number of PCPs in each group ordered CXR for screening over the past 12 months, but a larger proportion of PCPs aware of guidelines ordered LDCT (69% vs 36%, p<0.001) and initiated a discussion on screening (84% vs 59%, p<0.001) over the past 12 month. 14% of PCPs aware of guidelines reported that benefits of LCS were not clear to their patients compared with 43% of unaware physicians (p<0.001). Both groups of PCPs reported similar scores when questioned on other barriers to screening such as insurance coverage, risks of LCS, and cost to society. There were no differences between groups by practice size, training background, years in practice, or PCP demographics. Conclusion: Awareness of USPSTF recommendations for lung cancer screening is associated with the perception of benefit of LDCT and with increased utilization of LDCT for screening. Educational interventions for PCPs may improve adherence with LCS recommendations.

Keywords: cancer screening, survey research, lung cancer, low-dose CT

POSTER SESSION 1 - P1.03: RADIOLOGY/StAGING/SCREENING

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P1.03-054 QUANTITATIVE ACCURACY AND LesION DetECTABILITY oF LOw-DOSE FDg-PEt For LUNG CANCER SCREENING

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Background: Low-dose computed tomography (CT) screening for high-risk patients can reduce lung cancer mortality, but false positivity rates are high. Positron emission tomography (PET)/CT is more accurate compared to CT alone, but typically is associated with a higher radiation exposure. We investigate a low radiation dose PET/CT solution without compromising quality. Methods: Twenty lung cancer patients were scanned with PET/CT after an uptake period of 60 min, following injection of 5.9±0.14 mCi 18F-Fluorodeoxyglucose. All were scanned with 2 beds covering the lungs at 10 min each, resulting in 120±25 x106 mean true coincident counts per bed. Reduced doses were simulated by randomly discarding events in the PET list mode according to 9 predefined true count levels, from 20 to 0.25 x106. For each patient & simulated dose, the highest possible number of independent realizations was generated & reconstructed, up to 50. The reconstruction algorithm was OP-OSEM, using TOF and PSF, with 2 iterations, 21 subsets & 5mm smoothing, producing 600x400 image matrices with voxel size 2.044x2.044x2.033mm. At each simulated dose, lesions consistent with those of early lung cancer were identified & classified by metabolic volume, signal-to-background contrast, mean & max SUV, lesion-to-background SNR, & Hotelling observer SNR. Bias & stability of the lesion activity measurements were evaluated across all simulated dose levels, and detectability was determined by various human-trained, numerical observer models. Results: Twelve isolated lung lesions (mean volume 2.61±2.86 cm3) on CT were studied in detail. Analyses of bias & reproducibility in the lesion activity values showed that measurements were stable until the count levels approached extreme conditions. Bias in the lesion VOI mean & max SUV were relatively negligible until true count level was decreased to 1 million. Variance on reproducibility of lesion values showed a more dramatic trend, but standard deviation was still around 10% at 5 million counts. Conclusion: We show that simulated images with accurate lesion characteristics can be obtained at 1/12 of a typical radiotracer dose.

Keywords: low dose, lesion detectability, PET/CT, lung cancer screening
Background: Although lung cancer (LC) continues to be one of the leading causes of cancer morbidity and mortality world-wide, the NLST trial showed that low dose computed tomography (LDCT) screening can substantially reduce mortality in specific high-risk populations. However, most individuals are not making informed decisions which take into account the risks of screening although US guidelines advocate for informed decision-making. We report preliminary results of a web-based interactive LC decision aid (LuCaS DA) on LC screening knowledge and decision making compared to the US National Cancer Institute (NCI) Lung Screening Decision Aid. Methods: Individuals in the study (n=50; from rural Kentucky and SE Florida, USA) had an elevated risk for lung cancer (n=50) due to smoking. Participants completed a baseline survey and were randomized to viewing the LuCas DA or the NCI website. After 2 weeks, participants completed an online survey. Surveys collected information on demographics, health status, smoking history, knowledge of CT lung cancer screening, decisions about being screened for lung cancer, and decision conflict about screening. Results: Participants were 52.6 ± 5.9 years old on average; were majority female (77.1%), White (62.0%), and non-Hispanic (83.7%), and reported having some insurance coverage (88.0%). Most were current daily smokers (70.2%), and on average had smoked an average of 27.9 (SD 7.7) years. Mean Decisional Conflict overall participants was 39.3 (SD 13.5) at baseline and 34.4 (SD 11.1) at 2 week follow up, with no differences between the arms. The percentage of participants showed that they had made a decision about screening increased slightly from 32.2% at baseline to 37.5% at follow up. Preparedness for making a decision about screening (measured POST only) showed no differences between the arms. There were some increases in knowledge about CT screening and knowledge about LC5 guidelines from initial to 2-week follow up. Finally, a qualitative exploration of the LuCaS DA showed that it had high levels of acceptability. Conclusions: DAs can facilitate informed decisions about participation in cancer screening, and US policies have required their use. This is the first study that we are aware of that assess the use and effects of a lung cancer screening decision aid. These preliminary results show that the LuCaS DA can improve some outcomes, but not consistently more than the NCI webpages. Additional analyses will include the full sample of participants, evaluate a broader array of decision and behavioral outcomes, and consider longer term outcomes of the LuCas DA.

Keywords: decision aids, Lung cancer screening, decision-making

P1.03-056 IMPLEMENTATION OF A PROSPECTIVE BIOSPECIMEN COLLECTION STUDY IN AN ESTABLISHED LUNG CANCER SCREENING PROGRAM

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Background: Complexities such as addressing indeterminate pulmonary nodules (IPNs) are an inherent part of a lung screening program, and defining which individuals will benefit from invasive intervention is not always known. With the goal of combining non-invasive biomarkers with imaging to more definitively stratify patients, we initiated an investigational biospecimen collection process into our lung screening program. Ultimately, these biomarkers may improve specificity within the screening population, thereby reducing the overall cost and potential morbidity from false positive results of low-dose computed tomography scan (LDCT) screening. Studies like this are important to the ongoing improvement of lung cancer screening. Methods: NCCN high-risk individuals enrolled in a high volume clinical lung screening program were introduced to our IRB approved research biospecimen collection process into our lung screening program. Ultimately, 2044 individuals successfully accrued to a prospective diagnostic study and share specific biospecimens of adjustments were made, which significantly increased enrollment. This included implementation of a multidisciplinary taskforce consisting of research and clinical staff committed to patient outreach and participation. To date, samples from approximately 1620 subjects have been collected. Of these, 268 (19%) were found to have newly detected IPNs measuring 6.2-20mm on LDCT, and 28 samples were from patients with subsequent diagnoses of lung cancer. Conclusion: Successful coordination of biospecimen collection within a lung screening program is complex, but achievable with multidisciplinary coordination, and has great potential to help further stratify patients that may or may not benefit from invasive diagnostics and therapy. We demonstrate an established lung screening program that is successfully accruing to a prospective diagnostic study and share specific recommendations for how to successfully accrue in other programs.

Keywords: biospecimen, blood sample, Lung Screening, Indeterminate pulmonary nodule

P1.03-057 ASSESSMENT OF LUNG CANCER RISK- REGIONAL RESPIRATORY DISEASE SCREENING REPORT IN JILIN, CHINA

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Background: Both morbidity and mortality of lung cancer ranks first in China. According to the“2012 cancer registration report of China”, Northeast China has a high prevalence area of lung cancer, so early diagnosis of lung cancer is particularly important. Based on this, we made the regional survey in Changchun city. (1) To investigate the incidence of pulmonary nodules and lung cancer in Changchun city. (2) To provide the foundation of large data study on early screening of lung cancer and disease control. Methods: Carry out the investigation of the people over 50 years of age in 10 communities in Changchun of Jilin Province (A total of 1461 people), including questionnaire, pulmonary function tests and low-dose spiral CT examination. The disease assessment and patient management are based on “Diagnosis and treatment of pulmonary nodules in Chinese expert consensus”. Results: The percentage of lung disease in the investigated population was 25.67%, and the constitution of the lung disease included: 30.67% of the lung nodules, 37.07% of chronic obstructive pulmonary disease, 18.67% of inflammation, 5.6% of the lung, 2.13% of pulmonary interstitial fibrosis, 2.13% of pleural effusion and 3.73% of other lung diseases. The number of pulmonary nodules was 115, accounting for 7.87% of the total number of screening, 89 cases of solitary nodules, 26 cases of multiple nodules. A total of 4 patients with lung cancer were confirmed by pathology, including 2 cases of adenocarcinoma, 1 cases of squamous cell carcinoma and 1 case of mucinous carcinoma of the lung. All of the cancer cases were solitary nodules, and accounted for 3.48% of the total samples. Among them, 3 patients are male with a history of smoking, and 1 is female without any history of smoking. According to the nodule size, the diameters of nodule in 3 cases are greater than 8mm and 1 case is less than 4mm. According to the quality of nodules, 3 cases are solid and mixed nodules, and 1 case is ground-glass opacity. Conclusion: (1)Smoking is a risk factor for lung cancer. (2) Solid and mixed character nodules in pulmonary nodules and larger diameter nodules are more likely to develop into cancer, so they should be strengthened management. (3) Low-dose spiral CT is helpful for early diagnosis of lung cancer.

Keywords: Low-dose spiral CT, lung cancer, pulmonary nodules

P1.03-058 COST-EFFECTIVENESS OF CT SCREENING IN THE EARLY DETECTION OF LUNG CANCER

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Abstracts

Medicum, Nicolas Copernicus University in Torun, Bydgoszcz/Poland

Background: Screening using computerized tomography of the chest for an early detection of lung cancer has been performed worldwide since decades, but only two years ago, after proving in a prospective randomized study that it prolongs survival of the study population, it received the recommendation of scientific societies. However, the issue of cost-effectiveness of this screening remains open. Methods: A review of several cost-effectiveness analyses of oncology screening using low-dose CT available in the literature was performed. We also conducted our own cost-effectiveness analysis on the basis of epidemiological data and data from the National Health Fund concerning the type, number and cost of medical procedures reimbursed for lung cancer patients. Results: The results of cost-effectiveness analyses carried out in different countries are equivocal and depend mainly on the inclusion and exclusion criteria, methods of analysis and prices of medical procedures. More recent analyses, performed in different countries, indicate high profitability of this screening. In our study, the cost of early detection of one lung cancer using CT scan is comparable to the cost of a detection of one breast cancer using mammography and is about 3,600 Euro. The incremental cost-effectiveness ratio (ICER) in our analysis is about 1180 Euro/ life year gained. Conclusion: As the widely accepted limit of cost-effectiveness is three times the gross national product per capita / life year gained, lung cancer screening with low-dose CT in Poland should be considered highly cost-effective. In future screening programs, high cost-effectiveness can be achieved by strict adherence to inclusion and exclusion criteria. To ensure this, screening should be performed either as prospective observational non-randomized clinical trials or in dedicated screening centers. To ensure low level of false positive and false negative results, radiologists in screening centers should be equipped with software for measuring and monitoring the volume of pulmonary nodules.

Keywords: cost-effectiveness analysis, lung cancer screening, ICER, cancer screening

POSTER SESSION 1: P1.03: RADIOLOGY/STAGING/SCREENING SCREENING - MONDAY, DECEMBER 5, 2016

P1.03-059 ORGANIZED HIGH RISK LUNG CANCER SCREENING IN ONTARIO, CANADA: A MULTI-CENTER PROSPECTIVE EVALUATION

Martin Tammemägi, Joanne Hader, Monica Yu, Kiran Govind, Erin Svara, Marta Turcanc, Beth Miller, Gail Darling

Health Sciences, Brock University, St. Catharines/Canada, Cancer Care Ontario, Toronto/ON/Canada

Background: Guidelines published in Ontario Canada in 2013, recommend screening individuals at high risk of lung cancer with low-dose computed tomography through an organized program. Cancer Care Ontario, Ontario’s provincial cancer agency, is implementing a prospective evaluation of organized high risk lung cancer screening (HRLCS) in a 2-year, multi-centre pilot. The pilot evaluation aims to inform: Recommendations to Ontario’s Ministry of Health and Long Term Care regarding the potential for a provincial program. Optimal program design and requirements for effective implementation. Methods: The process to establish a robust evaluation plan for the HRLCS pilot included the development of a logic model, evaluation objectives and evaluation questions. Input from a multidisciplinary panel of experts, including clinicians, epidemiologists, and administrators guided the development of the evaluation plan. A modified Delphi technique facilitated panel input on the proposed evaluation questions, which were drafted based on the logic model and evaluation objectives, and aligned to the steps in the screening pathway. Panel members rated the importance of each evaluation question through an online survey using a 5-point Likert scale, and proposed changes or additional questions. A question was retained if >75% of panel members rated it as important or very important. A facilitated discussion post survey enabled a review of survey results to confirm consensus on the final set of evaluation questions. Results: The survey was completed by all panel members. Of 32 evaluation questions proposed, 31 were rated as important or very important by more than 75% of respondents. Endorsed questions addressed both screening processes and key outcomes, and included, for example: 1) Recruitment strategies engage individuals representative of the eligible population? 2) The follow-up processes occur as intended? 3) Screening identify early stage lung cancers? Panel discussion led to retention of the single question that did not meet the threshold, and the addition of one new question to the evaluation plan. Given consensus was achieved, a second round modified Delphi survey was not required. Conclusion: Using an expert panel and modified Delphi technique was an effective method to obtain consensus on the pilot evaluation questions. Endorsed evaluation questions will frame the development of measures and indicators to be assessed throughout the pilot. This comprehensive evaluation strategy will inform the design and implementation of a high quality organized HRLCS screening program.

Keywords: Evaluation, high risk lung cancer screening

POSTER SESSION 1: P1.03: RADIOLOGY/STAGING/SCREENING SCREENING - MONDAY, DECEMBER 5, 2016

P1.03-060 LUNG CANCER SCREENING: A QUALITATIVE STUDY EXPLORING THE DECISION TO OPT OUT OF SCREENING

Lisa Carter-Harris1, Susan Brandzel2, Joshua Roth3, Karen Wernli3, Diana Buist4

1School of Nursing, Indiana University, Indianapolis/IN/United States of America, 2Group Health Research Institute, Group Health, Seattle/WA/United States of America, 3Hutchinson Institute for Cancer Outcomes Research, Fred Hutchinson Cancer Research Center, Seattle/United States of America

Background: Lung cancer screening (LCS) with annual low-dose computed tomography is relatively new for long-term smokers in the US supported by a US Preventive Services Task Force Grade B recommendation. As LCS programs are more widely implemented and providers engage patients about LCS, it is critical to understand what influences the decision to screen, or not, for lung cancer. Understanding LCS behavior among high-risk smokers who opt out provides insight, from the patient perspective, about the shared decision-making (SDM) process. This study explored LCS-eligible patients’ decision to opt out of LCS after receiving a provider recommendation. New knowledge will inform intervention development to enhance SDM processes between high-risk smokers and their provider, and decrease decisional conflict about LCS. Methods: Semi-structured qualitative interviews were performed with 18 LCS-eligible men and women who were members of an integrated healthcare system in Seattle about their decision to opt out of screening. Participants met LCS criteria for age, smoking and pack-year history. Audio-recorded interviews were transcribed verbatim. Two researchers with cancer screening and qualitative expertise conducted data analysis using thematic content analytic procedures. Results: Participant mean age was 66 years (SD 6.5). Majority were female (61%), Caucasian (83%), current smokers (61%). Five themes emerged: 1) Knowledge Avoidance; 2) Perceived Low Value; 3) False Positive Worry; 4) Practical Barriers; and 5) Misunderstanding. Representative thematic example quotes are presented in the Table below.

Knowledge Avoidance

“It's fear of the unknown...if I know, you have to follow through and do more and more.”

Perceived Low Value

“It could show me if I had lung cancer...what are they going to do?...screening doesn't really make any difference…”

False Positive Worry

“I did schedule one...then after I read the print out, I canceled it...the false positives were so high. I thought why...that would be so stressful…”

Practical Barriers

“I really didn't have time to get over there.”

Misunderstanding

“I wasn't hurting or having any problems breathing...wasn't a top priority for me”[reflecting misunderstanding of the concept of screening]

Conclusion: Many screening-eligible smokers opt out of LCS. Participants in our study provided new insights into why some patients make this choice. LCS is effective in early lung cancer detection among high-risk patients. However, LCS has associated risks and harms making the SDM process critical. Understanding why people decide not to screen will enhance future efforts to improve knowledge transfer from providers to patients about the risks and benefits of LCS and ultimately enhance SDM about screening.

Keywords: health behavior, qualitative, decision making, lung cancer screening

POSTER SESSION 1: P1.03: RADIOLOGY/STAGING/SCREENING SCREENING - MONDAY, DECEMBER 5, 2016

P1.03-061 PATIENT MOTIVATIONS FOR PURSUING LOW-DOSE CT LUNG CANCER SCREENING IN AN INTEGRATED HEALTHCARE SYSTEM: A QUALITATIVE EVALUATION

Joshua Roth1, Susan Brandzel2, Lisa Carter-Harris1, Diana Buist3, Karen Wernli3

1Cancer Research Center, Seattle/United States of America

Background: Guidelines published in Ontario Canada in 2013, recommend screening individuals at high risk of lung cancer with low-dose computed tomography through an organized program. Cancer Care Ontario, Ontario’s provincial cancer agency, is implementing a prospective evaluation of organized high risk lung cancer screening (HRLCS) in a 2-year, multi-centre pilot. The pilot evaluation aims to inform: Recommendations to Ontario’s Ministry of Health and Long Term Care regarding the potential for a provincial program. Optimal program design and requirements for effective implementation. Methods: The process to establish a robust evaluation plan for the HRLCS pilot included the development of a logic model, evaluation objectives and evaluation questions. Input from a multidisciplinary panel of experts, including clinicians, epidemiologists, and administrators guided the development of the evaluation plan. A modified Delphi technique facilitated panel input on the proposed evaluation questions, which were drafted based on the logic model and evaluation objectives, and aligned to the steps in the screening pathway. Panel members rated the importance of each evaluation question through an online survey using a 5-point Likert scale, and proposed changes or additional questions. A question was retained if >75% of panel members rated it as important or very important. A facilitated discussion post survey enabled a review of survey results to confirm consensus on the final set of evaluation questions. Results: The survey was completed by all panel members. Of 32 evaluation questions proposed, 31 were rated as important or very important by more than 75% of respondents. Endorsed questions addressed both screening processes and key outcomes, and included, for example: 1) Recruitment strategies engage individuals representative of the eligible population? 2) The follow-up processes occur as intended? 3) Screening identify early stage lung cancers? Panel discussion led to retention of the single question that did not meet the threshold, and the addition of one new question to the evaluation plan. Given consensus was achieved, a second round modified Delphi survey was not required. Conclusion: Using an expert panel and modified Delphi technique was an effective method to obtain consensus on the pilot evaluation questions. Endorsed evaluation questions will frame the development of measures and indicators to be assessed throughout the pilot. This comprehensive evaluation strategy will inform the design and implementation of a high quality organized HRLCS screening program.

Keywords: Evaluation, high risk lung cancer screening

POSTER SESSION 1: P1.03: RADIOLOGY/STAGING/SCREENING SCREENING - MONDAY, DECEMBER 5, 2016
Background: Low-dose CT (LDCT) lung cancer screening for heavy smokers was given a ‘B’ rating by the US Preventive Services Task Force (USPSTF) in 2013, and gained widespread insurance coverage in the U.S. In 2015, Littke was about patient motivations for pursuing lung cancer screening outside of clinical trials because it is a relatively new covered service. The objective of this study was to understand some of the major factors that motivated patients to pursue LDCT lung cancer screening in an integrated healthcare system. Methods: We conducted a semi-structured qualitative interviews with 20 adult men and women who were members of an integrated healthcare system in Washington State about their choice to receive LDCT lung cancer screening. Participants met USPSTF screening criteria for age and smoking history. Training and obtained a total of 25 randomly selected eligible participants and completed interviews (80% response rate) in the Fall of 2015. The interviews were recorded, transcribed, and three investigators used inductive content analysis to identify themes about motivations for pursuing lung cancer screening. Results: Participant mean age was 68 years, 60% were male, 90% were Caucasian, and 35% were current smokers. Analysis of the transcripts identified 6 primary themes (Table 1) that were common motivations for pursuing LDCT lung cancer screening: 1) early-detection benefit, 2) limited understanding of LDCT harms, 3) relatively low radiation dose, 4) trust in the referring clinician, 5) friends and family with advanced cancer, and 6) low out-of-pocket cost.

Table 1. Participant quotes demonstrating motivations for pursuing low-dose CT lung cancer screening.

<table>
<thead>
<tr>
<th>Theme</th>
<th>Participant Quote</th>
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</table>
| Early-detection Benefit       | "I really have a very high stake in health and everything. I have a concern and a fear that I will get lung cancer. (If screening) would detect it (cancer) if I had it, it would give me the chance to deal with it before it gets worse."
| Low radiation dose            | "Everyone is very concerned about the low radiation dose in the screening test."
| Trust in the referring clinician | "I trust them (the doctors) a lot. I have known them for a long time and I trust them."
| Friends and family with advanced cancer | "My mother died of lung cancer when she was 57 years old. I don’t want the same to happen to me."
| Friends and family with advanced cancer | "My father died of lung cancer and my husband died of lung cancer. So when she said that I should go for screening, I didn’t have a choice."
| Low-out-of-pocket cost         | "If you had $100 in health insurance, it doesn’t mean anything, so what’s the point?"
| 'I would never bother you or put you down, because that doesn’t help you accomplish what you need to do. And nagging doesn’t help you either, but they need to talk to you and show real concern and let you know it."

Conclusion: The participants in our study were motivated to obtain lung cancer screening based on perceived benefit of early-detection, an absence of safety concerns, social factors, and low expense. Our findings provide new insights about patient motivations for pursuing LDCT lung cancer screening. Further research is needed to understand and improve lung cancer screening shared decision-making processes.

Keywords: false-positive, qualitative, Screening, computed tomography
**Abstracts**

**Keywords:** NLST, Radiomics, LDCT, lung cancer screening

**POSTER SESSION 1 - P1.03: RADIOLOGY/STAGING/SCREENING**

**SCREENING**

**MONDAY, DECEMBER 5, 2016**

**P1.03-064 CHEST X-RAY (CXR) SCREENING IMPROVES LUNG CANCER (LC) SURVIVAL IN THE PROSTATE LUNG COLON AND OVARY (PLCO) RANDOMIZED POPULATION TRIAL (RPT)**

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**Background:** The effectiveness of CXR-screening for LC was estimated in the context of performing a cost-effectiveness analysis of LC-screening comparing CT, CXR, and no screening. CXR-screening has long been considered ineffective. We because no RPT has demonstrated a LC mortality reduction. However, CXR-screening has been shown to produce a significant survival advantage not attributable to overdiagnosis or other screening biases (JCO:20;1973,2002). The lung portion of the PLCO trial, which compared CXR to no screening, reported no LC mortality reduction after 13-years follow-up (JAMA:306,1875, 2011). However, that analysis included all LCs diagnosed over 13-years, despite the fact that the active screening period lasted only 3-years. LC survival was not reported. Since screening is exceedingly unlikely to provide any advantage to individuals diagnosed many years after active screening is discontinued, and because sojourn time associated with CXR-screening is estimated to be up to 4 years, we evaluated outcomes of LCs diagnosed within 7-years of randomization in PLCO. Methods: PLCO randomized 77,445 subjects to an experimental (EG) undergoing a prevalence CXR and 3 annual incidence CARs and 77,456 others to an unscreened control group (CG). Using Kaplan-Meier methods in the intent-to-screen analysis of PLCO data, LC survival and mortality were calculated for all LCs diagnosed during the 13-year follow-up, as well as those diagnosed within 7-years of randomization. LC incidence and mortality were compared with Fisher’s exact test. Survival was compared with the log-rank test. All P-values are two-sided. Results: After 13-years, 1,838 and 1,737 lung cancers were detected in EG and CG, respectively (RR=1.06; 95% CI 0.99-1.13; p=0.09). Median survival was 12.2-months vs. 11.5-months, and 5-year survival was 24% vs. 19% in EG and CG respectively (p=0.0008). There were 1,217 and 1,203 LC deaths, indicating no LC mortality reduction (RR=1.01; 95% CI 0.93-1.09; p=0.77). Within 7-years of randomization, 1,072 and 1,022 lung cancers were detected in EG and CG, respectively (RR=1.05; 95% CI 0.96-1.14; p=0.27). Median survival was 14.5-months vs. 11.5months, and 5-year survival was 27% vs. 18% in EG and CG, respectively (p=0.0001). Among these cases, there were 764 and 811 LC deaths, indicating a trend toward reduced LC mortality that was not statistically significant (RR=0.96; 95% CI 0.85-1.14; p=0.26). Conclusion: In PLCO, randomization to CXR-screening produced a significant improvement in LC survival. This survival advantage cannot be attributed to any conventional screening bias including overdiagnosis. The benefit is diminished when lung cancers diagnosed well beyond the active screening interval are included in the analysis.

**Keywords:** Screening, survival, mortality, chest X-ray

**POSTER SESSION 1 - P1.03: RADIOLOGY/STAGING/SCREENING**

**STAGING**

**MONDAY, DECEMBER 5, 2016**

**P1.03-066 INCORPORATION OF A MOLECULAR PROGNOSTIC CLASSIFIER IMPROVES CONVENTIONAL NON-SMALL CELL LUNG CANCER TNM STAGING**

Johannes Kratz1, Nancy Cook2, Gawitt Woodard3, Kirk Jones4, Matthew Gubens5, Thierry Jahan6, Il-Jin Kim7, Biao He8, Michael Mann2, David Jablons2, Michael Mann2

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**Background:** Tumor size, nodal spread, and distant metastases form the basis of current non-small cell lung cancer staging. Despite undergoing a major revision in 2009, the poor outcomes of early-stage lung cancer patients relative to other solid tumors such as breast and colorectal cancer suggests that further improvement to our ability to stage non-small cell lung cancers is needed. In this study, we demonstrate the benefit of integrating a clinically validated molecular prognostic signature into conventional TNM staging. Methods: A new staging system integrating a 14-gene molecular prognostic classifier with TNM descriptors was developed using 332 patients with stage I-IIIB non-squamous, non-small cell lung cancer resected at the University of California, San Francisco. This staging system was subsequently validated on a separate multi-institutional international cohort of 1379 patients with stage I-IIIB disease. Reclassification measures were used to assess for improvements in calibration and discrimination beyond conventional TNM staging. Results: In the validation cohort, 78.2% of patients were reclassified using the new staging system. 73% of these patients were reclassified more accurately. The new staging system demonstrated improved measures of model fit including the modified Nagelkerke’s R² statistic as well as the c-index. In addition, incorporation of the molecular classifier resulted in a Net Reclassification Improvement of 16.6% (95% CI 7.9-25.2%) and a relative Integrated Discrimination Improvement of 27.3% (95% CI 6.4-49.4%). Kaplan-Meier analysis of overall survival after surgical resection demonstrated superior survival curve separation with the addition of the molecular classifier. Figure 1. Kaplan-Meier analysis of overall survival from time of surgical resection (A: TNM staging, B: TNM staging).

**Keywords:** 8th edition, validation, Staging, survival

**POSTER SESSION 1 - P1.03: RADIOLOGY/STAGING/SCREENING**

**SCREENING –**
Background: We compared the prognostic impact of 8E to 7E, using sequentially-defined surgical quality cohorts. Methods: We analyzed curative-intent resections for non-small cell lung cancer from 2009-2016 in a population based cohort from 4 Dartmouth Referral Regions in 3 US states. Patients were re-staged by 8E criteria. Survival analyses used Kaplan-Meier estimates and Proportional Hazards models with adjusted hazard ratios (aHR) controlling for age, histology, grade, and comorbidities. Results: 548 of 2226 patients were stage-redistributed: 525 (24%) up, 23 (1%) down-staged. The largest shifts were from IB to IIA (76/522 [15%]); IIA to IIB (238/251[95%]); IIIB to IIIA (88/217 [41%]); IIIA to IIIB (59/277[21%]). We found no difference in unadjusted survival in patients upstaged in IB compared with those remaining in IB (p=0.55). Patients upstaged from IIB to IIIA had similar survival to those remaining IIB (p=0.4884), but were similar to patients already IIIA by 7E (p=0.8152). However, patients upstaged from IIA to IIIB had worse survival than those remaining in IIA (p=0.0360). Sub-classification of IIA had no prognostic value when comparing IIA1 vs. IIA2 (p=0.74), but patients in IA3 had significantly worse survival than those in IIA2 (p=0.0177). 5-year survival estimates for IA (IA1-IIB) were 65%, 68%, and 61% in our cohort, compared to 92%, 83%, and 77% in the IASLC database. Adjusted models indicate 8E stage as a significant prognostic factor (p<0.0001), with increasing hazards of death with each progressive stage beyond IA2 (Table 1). This result was reasonably consistent as the quality of resection increased incrementally from: All Patients, excluding margin-positives, excluding margin-positives and pNX resections, excluding margin-positives and resections without mediastinal nodes (MedNX).

<table>
<thead>
<tr>
<th>IASLC 8th-Edition Stage</th>
<th>3-Year Survival Estimate (95% CI)</th>
<th>5-Year Survival Estimate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA1 (N=91)</td>
<td>0.80 (0.69-0.88)</td>
<td>0.65 (0.48-0.77)</td>
</tr>
<tr>
<td>IA2 (N=454)</td>
<td>0.80 (0.75-0.84)</td>
<td>0.68 (0.62-0.73)</td>
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<tr>
<td>IA3 (N=312)</td>
<td>0.71 (0.65-0.76)</td>
<td>0.61 (0.54-0.68)</td>
</tr>
<tr>
<td>IB (N=509)</td>
<td>0.67 (0.63-0.72)</td>
<td>0.55 (0.49-0.60)</td>
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<tr>
<td>IIA (N=81)</td>
<td>0.66 (0.53-0.76)</td>
<td>0.61 (0.48-0.72)</td>
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<td>IIB (N=375)</td>
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<td>IIIA (N=302)</td>
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<td>0.41 (0.34-0.48)</td>
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<tr>
<td>IIIB (N=62)</td>
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<td>0.29 (0.18-0.42)</td>
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<td>IVA (N=40)</td>
<td>0.44 (0.26-0.61)</td>
<td>0.44 (0.26-0.61)</td>
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Adjusted Hazard Ratios by Quality Parameters

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<th>All Patients (N=2195)</th>
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<th>Exclude Margin+/pNX (N=1939)</th>
<th>Exclude Margin+/MedNX (N=1656)</th>
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</thead>
<tbody>
<tr>
<td>IA1</td>
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<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>IA2</td>
<td>0.83</td>
<td>0.83</td>
<td>0.70</td>
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<tr>
<td>IA3</td>
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<td>1.11</td>
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<td>IB</td>
<td>1.30</td>
<td>1.26</td>
<td>1.11</td>
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<td>IIA</td>
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<tr>
<td>IIB</td>
<td>1.72</td>
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<td>1.69</td>
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<tr>
<td>IIIA</td>
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<td>3.76</td>
<td>3.43</td>
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<td>3.11</td>
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</table>

Conclusion: Incorporation of a molecular classifier of tumor biology offers substantial improvements to conventional TNM staging and encourages application of molecular prognostic classifiers into the refinement of TNM staging systems for other solid tumors.

Keywords: Prognosis, NSCLC, Staging, Molecular

POSTER SESSION 1: P1.03: RADIOLOGY/STAGING/SCREENING
STAGING – MONDAY, DECEMBER 5, 2016

P1.03-067 VALIDATION OF THE IASLC 8TH EDITION (8E) TNM CLASSIFICATION FOR NON-SMALL CELL LUNG CANCER BY THE QUALITY OF SURGICAL RESECTION IN A US COHORT
Matthew Smeltzer¹, Nicholas Paris¹, Carrie Felnèi¹, Cheryl Houston-Harris¹, Meredith Ray¹, Yu-Sheng Lee¹, Meghan Meadows¹, Edward Robbins², Sam Signore³, Chris Mutrie², Raymond Osarogiagbon²
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Conclusion: EE was generally supported by our data, although modifications for Stage IA1-HB patients were not fully evident, even in high-quality resections.
resections. The survival disparity with IASLC data suggests that unidentified confounding factors are impairing survival in this early-stage US NSCLC cohort.

Keywords: IASLC 8th Edition, 8th Edition, TNM, Staging

POSTER SESSION 1 - P1.03: RADIOLOGY/STAGING/SCREENING
STAGING – MONDAY, DECEMBER 5, 2016

P1.03-068 IMPACT OF POSITIVE PLEURAL LAVAGE CYTOMETRY OR MALIGNANT EFFUSION ON SURVIVAL IN PATIENTS HAVING LUNG RESECTION FOR NSCLC
Tomohiro Obata1, NAOYA YAMASAKI1, YUKA KITAMURA1, GO HATACHI1, TAKURO MIYAZAKI2, KEITARO MATSUMOTO1, TOMOSHI TSUCHIYA1, KAZUHIRO TABATA1, TAKEHIKO NAGASAKI1
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Background: Pleural lavage cytology (PLC) is the microscopic study of cells obtained from saline instilled into and retrieved from the chest during surgery for NSCLC. PLC is not reflected in the 7th TNM classification of lung cancer by the Union for International Cancer Control (UICC), although it is known that PLC-positive means worse prognosis.

The reason is that information regarding the treatment of PLC-positive patients is still limited. On the other hand, malignant effusion is categorized M1a, and reflect the grade of malignancy more. The aim of this study is to evaluate the possibility of being an established independent predictor of prognosis and the efficacy of intrapleural chemotherapy (IPC) in PLC-positive patients. Methods: 1,165 of the 1,473 lung cancer patients who underwent surgery had undergone PLC before thoracotomy, following by a complete resection (PLC-positive:41 patients) and 16 patients with malignant effusion were evaluated. The treatment was performed for 16 patients with malignant effusion and 27 patients with PLC-positive. After pulmonary resection, IPC was performed after surgery, and the pleural cavity was filled with cisplatin with a normal saline solution. The disease-free survival (DFS) and the overall survival (OS) of the patients were evaluated. Results: The pathological diagnosis showed that 41 patients (2.8 %) were positive for (or suspected to have) malignancy in their PLC. The univariate analysis showed that only T category and lymph node metastasis were significant predictors of a PLC-positive status. The 5-year overall survival in PLC-positive patients was 37 % and that in PLC-negative patients was 75 %. The univariate (p<0.01) analyses showed that the status of PLC was significantly associated with the overall survival. Correction for differences in survival were obtained in the earlier stages than stage IIA. Twenty-six of the 42 PLC-positive patients underwent IPC. The median survival time of the IPC group was 47.0 months and that of those without IPC was 17.4 months (p<0.01), respectively. But, there are no significant differences between these groups with respect of DFS and recurrent site. Conclusion: PLC should be considered in all patients with malignant effusion, and that of those without IPC was 17.4 monthes (p<0.01), respectively. But, due to small number of patients in M1b subgroup, the difference was not statistically significant (p=0.08). In spite of widespread metastatic disease in M1b-EGFR-m patients, they had longer mOS than M1b-EGFR-wt patients, with the lowest disease burden, 18.8 vs 14.4 months, respectively. Conclusion: EGFR mutational status has probably more important impact on mOS than the number of metastases or number of metastatic sites in NSCLC. Our results indicate that further analysis is warranted to address this issue.

Keywords: intrapleural chemotherapy, PLC, malignant effusion

POSTER SESSION 1 - P1.03: RADIOLOGY/STAGING/SCREENING
STAGING – MONDAY, DECEMBER 5, 2016

P1.03-070 THE IMPACT OF ADVANCES IN SYSTEMIC STAGING ON THE RATE OF METACHRONOUS AND SYNCHRONOUS METASTASES IN PATIENTS WITH LUNG CANCER
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Background: To quantify the impact of advances in systemic staging (i.e. from CT-based to PET-based over the last 20 years) on the rate of distant metastases detected at their time of initial diagnosis (synchronous) and sometime after initial diagnosis (metachronous) in patients with lung cancer. Methods: The Surveillance, Epidemiology, and End Results (SEER) database, representing 10 % of the US population was used to analyze lung cancers from 1988-2008. (a) The fraction of patients with overt synchronous metastases at diagnosis was noted. (b) Among patients without overt metastasis at diagnosis, their 5-year mortality rate was taken as an estimate of their rate of metachronous metastasis (as most deaths were due to distant metastases). (c) The overall rate of metastases (metachronous + synchronous) amongst all patients was computed. (d) The fraction of all metastases detectable at initial diagnosis (synchronous / synchronous + metachronous) was computed. Rates were computed for patient cohorts diagnosed in different time intervals from 1988-2010, to reflect the use of different staging methods over the 20-year interval. Results: (a) The rate of synchronous metastatic disease slowly increased from = 53% in the earlier years to 55% in 2008. (b) Among patients without overt metastasis at diagnosis, the rate of metachronous metastatic disease slowly decreased from = 73% in the earlier years to = 62% in 2008. (c) If one assumes that most of the metachronous metastatic lesions were present (but covert) at the time of the initial diagnosis of the primary disease, then one can estimate that = 83-87% of patients have micro/macrosynchronous metastatic disease at presentation (this rate is basically unchanged over time, but small changes over time may reflect the impact of systemic chemotherapy). (d) Among all patients with metastatic disease, = 60.4% of metastatic lesions were detectable clinically or with CT at the time of diagnosis in the pre-PET era, vs. = 66.6% of these lesions being detectable clinically or with CT and/or PET in the PET era. Conclusion: The addition of PET appears to have a small but measurable impact on the rates of synchronous and metachronous metastasis, resulting in stage migration from metastatic to synchronous (i.e. from covert to overt) metastases at the time of diagnosis. The addition of PET to the pre-treatment evaluation increases the ability to detect metastatic disease by = 6% (from 60.4 to 66.6%).

Methods: Database of 479 metastatic non-small cell lung cancer (NSCLC) patients, treated between 2009 and 2011, all tested for EGFR mutations, was retrospectively reviewed to categorize them into one of the new sub-groups according to new M descriptors. Medical records of 355 patients, among them 89 with EGFR mutations (EGFR-m), had sufficient information that allowed appropriate new categorisation. Results: After a median follow up of 53.9 months, median overall survival (mOS) of EGFR-m patients (20.6 months) was significantly longer than mOS of patients without EGFR mutations (18.3 months, p<0.007). Patients with the smallest disease burden (M1b sub-group) had the longest mOS among EGFR wild type patients (EGFR-wt) and EGFR-m patients, 14.4 months and 41.1 month, respectively. However, due to small number of patients in M1b subgroup, the difference was not statistically significant (p=0.08). In spite of widespread metastatic disease in M1b-EGFR-m patients, they had longer mOS than M1b-EGFR-wt patients, with the lowest disease burden, 18.8 vs 14.4 months, respectively. Conclusion: EGFR mutational status has probably more important impact on mOS than the number of metastases or number of metastatic sites in NSCLC. Our results indicate that further analysis is warranted to address this issue.

Keywords: new TNM classification, M descriptor, EGFR mutational status, survival

POSTER SESSION 1 - P1.03: RADIOLOGY/STAGING/SCREENING
STAGING – MONDAY, DECEMBER 5, 2016

P1.03-069 EGFR MUTATIONS HAVE GREATER INFLUENCE ON SURVIVAL THAN PROPOSED M DESCRIPTORS OF NEW TNM CLASSIFICATION FOR LUNG CANCER
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Background: The forthcoming 8th edition of TNM staging system for lung cancer proposes revision of M descriptor. No changes of M1a category is suggested, while further subclassification of M1b category into M1b (single distant metastatic lesion in single organ) and M1c (multiple distant metastatic lesions) is proposed. The limitations of new classification due to lack of information on EGFR and ALK status that significantly impact treatment response and outcome have been pointed out, however no further analysis addressing this issue has been published. Here we report the impact of EGFR mutation status on survival in view of new TNM classification system.
Keywords: PET, synchronous and metachronous metastasis

POSTER SESSION 1 - P1.03: RADIOLOGY/STAGING/SCREENING
STAGING – MONDAY, DECEMBER 5, 2016

P1.03-071 IMPACT OF VISCERAL PLURAL INVADION TO T DESCRIPTORS: BASED ON THE FORTHCOMING EIGHTH EDITION OF TNM CLASSIFICATION FOR LUNG CANCER
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Background: According to the forthcoming eighth edition of TNM classification, T descriptors and M descriptors will be subdivided. Visceral plural invasion of lung cancer has been known as a non-size-based T2 descriptor. However, the definition still lacks in detail, and its validation is not included. Methods: We retrospectively reviewed 1250 patients, who underwent curative surgical resection for non-small cell lung cancer at Juntendo University Hospital, between January 2008 and December 2014. Patients with pathologic N0 or N2 disease were excluded. We subdivided tumor size based on the eighth edition of TNM classification. Cumulative survival rates were evaluated by the Kaplan–Meier method. Statistical differences in survival status were evaluated using the log-rank test. Results: In tumor size of 0-4cm, overall survival was significantly different between pT1 and pT1p2 in each tumor size; 0-1cm (p=0.0001), 1-2cm (p=0.001), 2-3cm (p=0.007), 3-4cm (p=0.012). In tumor size of over 4cm, overall survival was not different between pT1p2 and pT1p2 in each tumor size; 4-5cm (p=0.825), 5-7cm (p=0.311), over 7cm (p=0.272). In tumor size of 4-5cm with pT1p2, a five-year survival rate was 60%. In tumor size of 0-4cm with pT1p2, a five-year survival rate was not significant different with in tumor size of 4-5cm with pT1p2; 0-1cm 50% (p=0.799), 1-2cm 71% (p=0.169), 2-3cm 70% (p=0.370), 3-4cm 67% (p=0.609). Conclusion: In pathologic N0 disease, there was no prognostic difference between tumor size of 0-4cm with pT1p2 and 4-5cm with any pT. In this study, tumors 4cm or less with visceral plural invasion become classified as T2b, and tumors larger than 4cm but 5cm or less also become classified as T2b regardless of visceral plural invasion.

Keywords: visceral plural invasion, the eighth edition of TNM classification for lung cancer

POSTER SESSION 1 - P1.03: RADIOLOGY/STAGING/SCREENING
STAGING – MONDAY, DECEMBER 5, 2016

P1.03-072 MEDIASTINAL LYMPHNODES STAGING BY PET CT FOR RESECTABLE NON-SMALL CELL LUNG CANCER IN A TUBERCULOSIS ENDIMIC COUNTRY
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Background: TB is a major health problem in India, incidence is around 2.1 million patients in a tuberculosis-endemic country. Methods: Prospective assessment of the diagnostic efficacy of integrated PET-CT for detecting mediastinal lymph node metastasis was performed from February 2012 to February 2016. A total 160 patients underwent surgery for pathologically proven NSCLC. Patients who received chemotherapy or radiotherapy prior to surgery were excluded from study. Thus assessment of the diagnostic efficacy of integrated PET-CT for detecting nodal metastasis was performed in 46 patients (Male to Female ratio:4:1, mean age: 55 years). Patients underwent an integrated PET-CT examination and subsequent surgical nodal staging. One radiologist and 1 nuclear medicine specialist together prospectively evaluated PET-CT datasets. Nodes showing greater 18F-FDG uptake at PET without benign calcification or high attenuation >70 household unit (HU) at unenhanced CT were regarded as being positive for malignancy. All patients underwent hilar and mediastinal lymph nodes dissection according to the AJCC lymph node map (nodal stations 2R, 3R, 4R, 7, 8 and 9 for a right-sided tumour; 4L, 5, 6, 7 and 9 for a left-sided tumour) after resection of the main tumour. Histologic nodal assessment results were used as reference standards. Of these 55 patients, 10 (20%) had a past history of pulmonary tuberculosis as determined by clinical or imaging studies. Results: Of 230 mediastinal nodal stations evaluated in 46 patients, 2 (2%) stations in 48% patients proved to be malignant by histopathologic assessment. Mean number of lymph node stations evaluated were 5. On a per-nodal station basis, the overall sensitivity, specificity, accuracy, PPV, NPV of PET-CT were 60%, 97%, 96%, 38%, 99% for mediastinal lymph nodes staging(N2) respectively. Conclusion: Integrated PET-CT provides high specificity and high accuracy, but low sensitivity for mediastinal staging of NSCLCs. The high specificity is achieved at the expense of sensitivity by interpreting calcified nodes or nodes with high attenuation at CT, even with high FDG uptake at PET, as benign in a tuberculosis-endemic region.

Keywords: NSCLC, PET CT, Mediastinal lymphnode staging

POSTER SESSION 1 - P1.03: RADIOLOGY/STAGING/SCREENING
STAGING – MONDAY, DECEMBER 5, 2016

P1.03-073 PREDICTORS FOR PATHOLOGICAL N1 AND N2 DISEASE IN CLINICAL N1 NON-SMALL-CELL LUNG CANCER
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Background: Patients with clinical N1 (cN1) non-small-cell lung cancer (NSCLC) is usually considered to be candidates for curative resection. However, they sometimes have unexpected mediastinal nodal involvement (pN2). To avoid futile pulmonary resection, accurate preoperative evaluation of nodal status would be necessary. The purpose of this study was to identify predictors for lymph node metastasis in cN1NSCLC patients. Methods: We retrospectively reviewed data on the clinicopathological and radiological features of 170 patients with cN1 NSCLC who had undergone complete resection at Nagoya University Hospital between 2004 and 2015. Hilar and/ or intrapulmonary lymph nodes with ≥ 1.0 cm in the short axis on computed tomography or with high accumulation of [18F]Fluorodeoxyglucose (FDG) in positron emission tomography compared with that of the adjacent mediastinal tissue were considered as cN1 in our institution. The association between clinicoradiological variables and nodal status was analyzed to identify predictors for lymph node metastasis. Results: The cohort consisted of 125 males and 45 females, ranging in age 39 to 84 years. There were 62 (36%) adenocarcinomas, 82 (48%) squamous-cell carcinomas, 10 (6%) large-cell carcinomas, and 16 (10%) other types of cancers. The breakdown by pathologic N category was 61 (36%) pN0, 72 (42%) pN1, and 37 (22%) pN2 patients. Among pN2 patients, only three showed negative N1 lymph nodes (skip pN2 metastasis). Female gender, adenocarcinoma histology, middle or lower lobe origin and positive N1 lymph node (pN1) were significantly associated with pN2 by univariate analysis. Logistic regression analysis showed that the female and pN1 were significant predictor for pN2 with the odds ratio of 3.0 and 13.1, respectively (P = 0.02 and 0.001, respectively). In addition, using the 63 patients extracted from our cohort of this study, we sought the predictor of pN1. The maximum size of the lymph node and standardized uptake value of the FDG were significant factor for pN1 with the cut-off value of 1.3 cm and 4.28, respectively. Conclusion: Female gender and pN1 was significantly associated with pN2 in cN1 NSCLC patients of our cohort. The large size and a high accumulation of FDG of hilar or intrapulmonary lymph node might predict the pN1.

Keywords: lymph node, Non-small-cell lung cancer, cN1

POSTER SESSION 1 - P1.03: RADIOLOGY/STAGING/SCREENING
STAGING – MONDAY, DECEMBER 5, 2016

P1.03-074 COMBINED USE OF PET/CT AND CLINICAL FEATURES – YIELDS A HIGHER DIAGNOSTIC RATE OF MEDIASTINAL LYMPH NODE METASTASIS IN LUNG ADENOCARCINOMA
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Background: The aims of this study were to investigate the correlation
between 18F-fluorodeoxyglucose (FDG) uptake of the primary tumor and mediastinal lymph node metastasis (MLNM) in lung adenocarcinoma, and to improve the diagnostic capability of tumor FDG uptake and other risk factors in preoperatively occult MLNM preoperatively. Methods: We reviewed 360 consecutive pulmonary adenocarcinoma patients who underwent preoperative PET/CT scan and subsequent surgery. Resected tumors were classified according to the 2011 IASLC/ATS/ERS classification. Univariate and multivariate analysis were conducted to evaluate the associations between clinicopathological variables and MLNM. The receiver operating characteristic (ROC) curve analysis was performed to quantify the predictive value of these factors. Results: Of all the 360 patients, 54 were pathological N2 diseases. On univariate analysis, CEA level, nodule type, nodal SUVmax, tumor SUVmax, size, location and histologic subtype were associated with MLNM. On multivariate analysis, CEA ≥ 5.0 ng/ml (p < 0.001), solid nodule (p = 0.012), tumor SUVmax ≥ 3.7 (p = 0.027), nodal SUVmax ≥ 2.0 (p < 0.001) and centrally located tumors (p = 0.035) were independent risk factors that associated with MLNM. The area under the ROC curve (AUC) for tumor SUVmax in predicting MLNM was 0.764 and AUC of nodal SUVmax was 0.730. The combined use of five factors yielded a higher AUC of 0.885 for N2 disease. The tumor SUVmax among histologic subtypes differed significantly (p < 0.001). Conclusion: Primary tumor SUVmax of PET/CT was shown a good predictor for MLNM in patients with lung adenocarcinoma, and the underlying mechanism may attribute to the close association between tumor FDG uptake and IASLC/ATS/ERS adenocarcinoma subtypes. The combined use of tumor SUVmax factors with nodal SUVmax, solid nodule, centrally located tumor and increased CEA level improved the diagnostic capacity for predicting N2 disease preoperatively.

Keywords: histologic subtype, lung adenocarcinoma, PET/CT, Mediastinal lymph node metastasis

P03-075 PREDICTIVE FACTORS FOR MINIMAL PLEURAL DISEASE DETECTED AT THORACOTOMY OR POSITIVE LAVAGE CYTOLOGY

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Background: Minimal pleural disseminations and malignant pleural effusion is eventually diagnosed at the therapeutic thoracotomy. Pleural lavage cytology is another prognostic factor which is available through surgery. Although CT image have become high quality, prediction of such pleural disease is still difficult. To establish predictive markers for minimal pleural disease before surgery will be useful for planning strategy for the patients with minimal pleural disease. Methods: 115 patients who underwent pulmonary resection in our hospital from January 2010 to December 2011 were retrospectively analyzed for their clinicopathological information such as tumor marker CT image, and histology. 65 were male and 50 female. Histology was squamous cell carcinoma, adenocarcinoma, and other histology for 32, 78, and 5 cases, respectively. Clinical staging according to WHO 7th edition stage IA, IB, IIA, IIB, and IIA for 62, 31, 11, 3, and 8 cases, respectively. CT findings such as pleural indentation and contact of tumor on pleura were carefully measured on thin-slice CT sections with 0.5-1mm pitch. P value less than 0.05 was regarded as statistically significant. Results: Eight cases were positive for pleural disease, one for malignant effusion, 2 for minimal dissemination, and 6 for pleural lavage cytology. By statistical analysis regarding association between clinicopathological factors pleural disease, statistical positive factor was tumor diameter and CEA positivity (P=0.037 and 0.01, respectively), but tumor contact or tumor size did not reach a statistical significance (p=0.07). Pleural indentation and histologic type was not statistically significant. Conclusion: Based on current study, tumor diameter and serum CEA level could be possible predictive factors for minimal pleural disease. Upon limited number of patients, further study will be needed.

Keywords: pleural dissemination, pleural lavage cytology, CT, malignant effusion

P03-076 NODAL STAGING OF PATIENTS WITH PULMONARY MALIGNANCIES - THE PREDICTIVE VALUE OF DIFFERENT PATTERNS OF MEDIASTINAL 18FDG-PET ACTIVITY

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Background: In patients with pulmonary malignancies, 18FDG uptake in mediastinal nodes is a sensitive but non-specific indicator of metastatic disease. The pattern of tracer uptake may improve the predictability of such findings. Methods: To retrospectively i) compare 18FDG-PET scans and EBUS findings in patients with documented pulmonary malignancies; and, ii) compare the pattern of 18FDG uptake in mediastinal nodes in patients with /without documented mediastinal node metastases. Methods: 62 patients with documented pulmonary malignancies underwent 18FDG-PET scintigraphy followed by EBUS within the ensuing 3 weeks. One-two nodes were assessed in each patient, determined by 18FDG-PET findings and accessibility of the FDG-positive nodes. The mediastinal nodal status from each procedure was compared. Results: EBUS resulted in mediastinal nodal status downgrading in 25 (40%) patients. No upgrading was noted. Downgrading most likely occurred when there several non-enlarged lymph nodes of similar 18FDG-avidity distributed randomly and bilaterally in the mediastinum, often with bilateral hilar uptake (17 of 25 patients). Further, only 2 of 19 patients exhibiting such a pattern of mediastinal tracer distribution were found to have hilev node metastases (10%), and both had metastatic disease elsewhere on the PET scan. 21 of 23 patients with positive EBUS findings demonstrated discrete 18FDG-avid lymph nodes ipsilaterally, with minimal-to-no 18FDG-avid nodes contralaterally. EBUS findings in 14 (23%) patients were inconclusive, despite multiple sampling. Enlarged, rounded lymph nodes with avid FDG uptake (SUV>4) were also likely to harbour metastatic disease. Conversely, a Hounsfield unit of >55 was associated with benign disease. Conclusion: The pattern of mediastinal 18FDG uptake was highly predictive of metastatic disease, and may circumvent the need for EBUS evaluation. Prospective analysis of these parameters will be undertaken.

Keywords: FDG-PET, Mediastium, Staging, EBUS
P1.03-078 SIZE MATTERS... BUT DON’T UNDERESTIMATE THE POWER OF MORPHOLOGY
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Background: The detection of solitary pulmonary nodules has increased due to the widespread use of Computed Tomography (CT) and will increase even more in the future when lung cancer screening will be embedded in daily practice. In addition to the clinical information, size is one of the most important parameters to assess the likelihood of malignancy. Although there is a considerable overlap in imaging characteristics of benign and malignant solitary pulmonary nodules, the power of morphology—even in small nodules—should not be underestimated. The aim of this pictorial essay is to give an overview of the wide range of morphologic characteristics and to address the available evidence on sensitivity and specificity of these characteristics.

Methods: Cases presented were collected during the Multidisciplinary Thoracic Oncology Tumor Board between January 2014 and May 2016. All malignant cases have histopathologic proof, whereas benign lesions were included when the benign nature was suggested after follow-up, negative PET-scan and/or multidisciplinary consensus. Results: With regard to margin characteristics, spiculation is highly suggestive of a malignant nature. It is the only feature that is incorporated as 'morphic' variable in most risk prediction models. Other features however may also be strong indicators of malignancy. Lobulation, halo sign, pleural indentation, vascular convergence sign and pitfall sign are frequently encountered in malignant nodules. The nodule-bronchus relationship can give additional information regarding the nature of the nodule, with signs such as air bronchogram, bubble like lucencies and bronchus cutoff sign being indicative of a malignant nature. In cavitated nodules, a very thin wall might indicate a benign cause, whereas a very thick wall is more common in malignant nodules. Calcification is typically seen in benign nodules, but depending on the calcification pattern a malignant etiology cannot be excluded. The presence of fat is a relative unreliable sign of benignity. In section CT will enable detection of subtle findings. Nodules rarely present with only one characteristic and combination of findings can definitely increase the likelihood of a correct diagnosis. Conclusion: The management of solitary pulmonary nodules involves both clinical and imaging assessment. Although a great overlap exists in morphologic features of benign and malignant nodules, thorough knowledge and recognition of subtle morphologic findings will aid in early detection of nodules with a high likelihood of malignancy and will avoid unnecessary follow-up and delay in diagnosis and treatment.

Keywords: morphology, lung cancer, solitary pulmonary nodule, computed tomography

P1.03-079 ADEQUACY OF PERCUTANEOUS LUNG BIOPSY FOR ASSESSING CLINICALLY REQUESTED GENETIC MUTATIONS IN LUNG CANCER
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Background: Percutaneous lung biopsy is used to assess for the presence of actionable genetic mutations in EGFR, BRAF and KRAS. ALK mutation was assessed separately through FISH, which was not assessed in this study. Sequencing can be performed with next generation sequencing (NGS) or single gene sequencing (SGS). Methods: A retrospective study with 188 consecutive histologically diagnostic CT guided lung biopsies sent for NGS were performed between 2013 and 2014. Procedures were performed using 18Gauge guiding cannula, 20 gauge side-cutting core needles and 22 gauge Chiba FNA needles. Patients in whom 2 or more gene mutation analyses were requested had their biopsy specimen analyzed for adequate tumor cellularity (>20% tumor) and if adequate had DNA extracted and sequenced with a 50-gene multiplex platform (Ion Torrent Personal Genome Machine). If the material was not adequate for NGS, the requested gene mutation analyses were performed with SGS. Demographics, procedure technique as well as lesion features were collected. Descriptive statistics were tabulated and chi-square statistical analysis performed. Results: 57.44% of the patients were female, with average age of 67 years (35-91) and 65.42% had history of smoking. Lesion size varied from 0.8 cm to 15.6 cm, with average of 3.9 cm. 83.51% were spiculated, 78.72% solid, 12.23% presented intralobular low attenuation (<20HU), 11.17% were associated with perilesional atelectasis and 19.14% with pleural effusion. 63.83% had known metastasis at the time of the procedure, 29.78% had systemic treatment before the biopsy. Specimens were successfully used for NGS in 80.52% of cases. Overall adequacy of biopsy specimens for analysis of gene mutations requested was 87.76%. Conclusion: The overall success rate of percutaneous image guided lung cancer biopsies for clinically requested genetic mutation analysis was 87.76%.

Keywords: Percutaneous lung biopsy, Single gene sequencing, next generation sequencing

POSTER SESSION 1 - P1.03: RADIOLOGY/STAGING/SCREENING STAGING – MONDAY, DECEMBER 5, 2016

P1.03-080 THE SUVMAX RATIO OF TWO TUMORS ON PET/CT MAY DIFFERENTIATE SEPARATE PRIMARY LUNG CANCERS AND INTRAPULMONARY METASTASES
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Background: Differentiation between separate primary lung cancers and intrapulmonary metastases (IM) has significant therapeutic and prognostic implications in lung cancer patients with multiple pulmonary nodules. In this retrospective study, we investigated the diagnostic ability of ratio (MSR) and differences (MSD) of maximum standardized uptake values (SUVmax) between two tumors in discriminating separate primary lung cancers from metastases. Methods: We evaluated 5641 lung cancer patients between March 2009 and March 2016 at the Chinese People’s Liberation Army General Hospital. Patients underwent PET/CT and pathology confirmed as multiple lung cancers were included. Patients with ground glass opacity lung cancers or underwent preoperative radiotherapy or chemotherapy were excluded. All lung cancers tissues were reassessed and discriminated from separate primary lung cancers to metastases by two pathologists independently according to comprehensive histological assessment criteria, which was proposed by IASLC lung cancer staging project as pathologic definition to distinguish multiple primary lung cancers from metastatic in the forthcoming eighth edition TNM classification of lung cancer. The MSR and MSD were determined and compared in diagnosing separate primary lung cancers. Receiver-operating characteristic (ROC) curve analysis was performed to determine the area under the curve (AUC), sensitivity and specificity with an optimal cut-off value. Example of MSR and MSD deduction was given in Figure 1.

Keywords: PET/CT, SUVmax, Multiple Primary Lung Cancers, Intrapulmonary Metastases

POSTER SESSION 1 - P1.03: RADIOLOGY/STAGING/SCREENING STAGING – MONDAY, DECEMBER 5, 2016

P1.03-081 THE SUVMAX RATIO OF TWO TUMORS ON PET/CT...
Results: Totally 24 patients with 24 pairs-tumor (18 primary, 6 metastases) were included. The area under the curve of MSR (AUC, 0.843; 95% CI, 0.637-0.958; p<0.001) was significantly higher than MSD (AUC, 0.685; 95% CI, 0.465-0.857; p=0.240) with p value 0.022. The optimal cut-off value for MSR and MSD was 1.61 (83.33% sensitivity, 83.33% specificity) and 1.94 (83.33% sensitivity, 66.67% specificity). Conclusion: The MSR from PET/CT may helpful in differentiating separate primary lung cancers from intrapulmonary metastases and larger studies were needed to confirm this result.

Keywords: diagnosis, Maximum Standardized Uptake Values, Separate primary lung cancers, Intrapulmonary metastases

Poster Session 1: P1.03: Radiology/Staging/Screening Staging – Monday, December 5, 2016

P1.03-081 SYNCHRONOUS TRIPLE MALIGNANT TUMORS OF THE LUNG: A CASE REPORT OF TWO LUNG ADENOCARCINOMAS, AND MUCOSA-ASSOCIATED LYMPHOID TISSUE LYMPHOMA
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Background: Synchronous primary malignant tumors are relatively rare. The accurate diagnosis remains challenging. Methods: We report a case of synchronous triple primary tumors of the right lung in a 64-year-old male patient in whom each tumor presented distinct CT imaging findings. Abnormal nodules were found in the lung (one in right upper lobe and another in the right lower lobe). Almost 2 years later, Chest CT revealed that the nodule in the right lower lobe had grown. After complete resection, pathological sections revealed the similar pathological features of two adenocarcinomas. As the L858R mutation within exon 21 of the EGFR gene was identified in the lower lobe tumor but not in the upper-lobe tumor, we diagnosed as double primary lung adenocarcinomas. We performed the right lower lobe tumor. Pathological examination revealed a combined adenocarcinoma and mucosa-associated lymphoid tissue (MALT) lymphoma.

Results: This is the first case of triple malignant tumors (two lung adenocarcinomas, and MALT lymphoma) reported in the literature. Conclusion: Because of its rarity, MALT lymphoma should be considered in the differential diagnosis when we encounter abnormal nodules in patients with synchronous malignant tumors of the Lung. Mutational analysis of the EGFR gene provided important information not only in decision-making of selection of chemotherapeutic agent but also in the diagnosis of double primary cancers.

Keywords: EGFR mutation, lung adenocarcinoma, Synchronous Triple Malignant Tumors, mucosa-associated lymphoid tissue lymphoma

Poster Session 1: P1.03: Radiology/Staging/Screening Staging – Monday, December 5, 2016

P1.03-082 18F-FDG PET/CT VALUE STAGING NSCLC EXTENSION TO THE LYMPH NODES, SINGLE CENTER EXPERIENCE
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Background: Non small-cell lung carcinoma (NSCLC) is the most common type of lung cancer. Correct clinical and pathological lymphnode (N) staging is helpful in differentiating separate primary lung cancers from intrapulmonary metastases and larger studies were needed to confirm this result. Results: This is the first case of triple malignant tumors (two lung adenocarcinomas). Correct clinical and pathological lymphnode (N) staging – 57,14%, positive predictive value – 40%, negative predictive value – 60%.

Estimated specificity of PET/CT for N staging of NSCLC was 25%; sensitivity – 57,14%, positive predictive value – 40%, negative predictive value – 60%.

Conclusion: Despite many advantages, PET/CT still has limited value staging NSCLC. Significant number of inaccuracies in N staging may occur evaluating inflammatory lymph nodes. The necessity of histologic confirmation of N stage in stage-I-III NSCLC is crucial as these patients may have surgical treatment combination and better outcomes.

Keywords: PET/CT, NSCLC, Staging

Poster Session 1: P1.03: Radiology/Staging/Screening Staging – Monday, December 5, 2016

P1.03-083 ADVANCES IN SURGICAL STAGING OF NSCLC
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Background: Staging of mediastinal lymph nodes in NSCLC defines the extent of thoracic malignancies & the disease process. It is based on the American Joint Committee for Cancer (AJCC), TNM staging system, which describes the best anatomic extent of the disease. This defines operability & surgical resectability, neoadjuvant therapy & predicting prognostic survivability.

Methods: A well-conducted literature search & review undertaken. All papers or studies in the last 10 years were identified and studied. Results: Surgical & non-surgical staging methods were identified, compared and analysed for their sensitivity & specificity. Size, location & characteristics of tumour, local invasion or extension, lymphadenopathy & metastatic disease spread were identified as parameters. Conclusion: Early accurate staging improves overall outcomes if therapeutic interventions are well-organised & executed in a timely fashion. Careful selection of staging methods is crucial.

Keywords: NSCLC, Staging, Surgical staging

Poster Session 1: P1.03: Radiology/Staging/Screening Staging – Monday, December 5, 2016

P1.03-084 IMPLICATIONS OF 8TH EDITION TNM PROPOSAL: INVASIVE VS. TOTAL SIZE FOR T DESCRIPTOR IN PTA1-2BNM0 LUNG ADENOCARCINOMA
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Background: The aim of this study was to conduct a clinicopathological comparative analysis of total tumor versus invasive tumor size in pT1a-2BNM0 nonmucinous lung adenocarcinomas. Methods: Resected pT1a-2BNM0 lung adenocarcinomas (1995-2012) based on 8th edition of TNM classification using total (N=1475) and invasive tumor size (N=1482) were included. Recurrence free probability (RFP) and lung cancer-specific survival (LCSS) were compared between both pT-staging systems using Kaplan-Meier method. Results: Use of invasive size for the T descriptor increased the number of pT1a tumors by 2 fold compared to use of total tumor size (316 vs. 161), with no difference in RFP and LCSS (RFP, 82% vs. 80%; LCSS, 94% vs. 93%). Use of invasive rather than total size also showed better stratification of lymphatic/vascular invasion and high grade histological subtypes according to increasing pT stage. RFP and LCSS in invasive-size-based pT2b were lower than those in total-size-based pT2b (RFP, 44% vs. 60%; LCSS, 69% vs. 77%). Conclusion: In pT1a-2BNM0
nonmucinous lung adenocarcinoma, the 8th edition TNM proposal to use invasive rather than total size for the pT descriptor gives better prognostic discrimination by capturing a larger number of patients with favorable prognosis (pT1a) and providing better stratification for pT2b.

as surgical specimen with histological type of adenocarcinoma and NSCLC NOS (Not Otherwise Specified) were routinely analyzed independent of the tumor stage and clinical characteristics (reflex testing) for these genetic alterations. Since January 2010 the EGFR mutation detection was performed with the EGFR Mutation Test Kit from ROCHE on a COBAS4800. Since August 2011 tumor tissue was analyzed for EML4-ALK with a two-step procedure. First an immunohistochemical staining was done with the Ventana anti ALK(D5F3), OptiView DAB IHC DetectionKit and OptiView AmplifikationKit and further on positive cases were tested by PCR (AmoyDx EML4-ALK FusionGeneDetectionKit) or ALK FISH (dual colour breakapart FISH/Abbott Vysis). Since January 2014 the tumor tissue was analyzed for ROS1 with a two-step procedure. First an immunohistochemical staining was done with ROS1 D4D6, cell signaling and further on positive cases were tested by PCR (AmoyDx EML4-ALK FusionGeneDetectionKit) or ALK FISH (ROS1 (E6-Q22) dual colour breakapart probe ZytoVision). Braf testing was performed using the cobas®©4800BRAF V600Mutation Test from Roche since March 2016. Results: An EGFR Mutation was found in 340 out of 2776 patients (12.2%). 253 patients (9.1%) carried an activated mutation (Exon 19 Deletion, Exon 21 L858R). EML4-ALK positive translocation was found in 100 out of 2212 patients (4.5%).

ROS1 positive translocation was found in 5 out of 1060 patients (0.5%). BRAF mutation was found in 3 patients out of 75 (4.0%). The frequency of these genetic alterations in Austrian patients with NSCLC was quite similar to other Caucasian peers. Therefore reflex testing is recommended independent of any clinical characterization.

Keywords: Non-small-cell lung cancer, Target therapy

POSTER SESSION 1 - P1.04: PULMONOLOGY – MONDAY, DECEMBER 5, 2016

P1.04-001 EGFR, EML4-ALK, ROS1 AND BRAF TESTING IN AUSTRIAN PATIENTS WITH NSCLC: A MULTICENTRE STUDY

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Background: Targeted therapy is becoming increasingly important and has improved the overall survival for patients with NSCLC. EGFR and BRAF mutations, EML4-ALK and ROS1 translocations are current allocatable targets. The incidence of these druggable targets in Austria is unknown. Methods: Tumor tissue from bronchoscopy, CT- and ultrasound guided biopsies as well

Keywords: TNM staging, T factor, Invasive adenocarcinoma, Tumor size
Conclusion: A tendency towards enlargement and improved segmentation of airways is seen with the use of CPAP in both levels of pressure. However, the power of this pilot study is limited and larger studies might be encouraged. Funded by La MaratóTV3-20133510, FIS PI10/09097, DPI2015-65286-R, 2014-SGR-1470, PROD-2014-00065, FUCAP and SEPAR.

Keywords: Thorax CT, diagnosis, Peripheral Pulmonary Nodule

Poster Session 1: P1.04: Pulmonology • Monday, December 5, 2016

P1.04-003 INCIDENCE OF NON-CASEATING GRANULOMAS DIAGNOSED IN PET AVID MEDIASTINAL/HILA NODES IN PATIENTS WITH KNOWN BREAST CANCER

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Background: Breast cancer is known to metastasize to the lung. Most breast malignancies are clinically staged using radiographic modalities (e.g. PET scans). Importantly, many inflammatory disorders will present similar lymph node FDG uptake on PET-as that of metastasized breast cancer. The latter confuses the treatment for individuals within whom both undiagnosed autoimmune disorders and breast cancer co-occur. We aim to examine the frequency of non-caseating granulomas diagnosed in PET avid mediastinal/hilar nodes in patients with known breast cancer. Methods: Between March 2013 and December 2015, 46 patients diagnosed with breast cancer were staged by PET-CT. Those with positive result in the mediastinum/hilum underwent linear endobronchial ultrasound (EBUS) for pathologic diagnosis and ensuing treatment Results: Of the 46 patients with avid mediastinal/hilar adenopathy, 31 (67.4%) had malignant cytology on EBUS; the remaining 15 had non-caseating granulomas. Conclusion: Conclusion: This study represents our casuistry, the objective was achieved in all the patients that underwent the procedures such as tracheobronchial recanalization and extraction of tracheal, bronchial or pulmonary tissue with a significant symptomatic improvement with a low risk and low morbidity.

Keywords: bronchoscopy, recanalization, lung cryosurgery

Poster Session 1: P1.04: Pulmonology • Monday, December 5, 2016

P1.04-005 EFFICACY OF PHOTODYNAMIC THERAPY COMBINED WITH A GUIDE SHEATH METHOD IN LUNG CANCER PATIENTS WITH ENDOBRONCHIAL STENOSIS

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Background: Photodynamic therapy (PDT) using a second generation of photosensitizer, talaporfin sodium was useful for the curative or palliative treatment of lung cancer. However, it is required for interventional pulmonologist to perform accurate PD-laser irradiation in some lung cancer case. We hypothesized that all-direction type PD-laser probe covered with a guide sheath (GS) (GS-PDT) made it possible to secure its probe and fix its position in the endobronchial lesion, to enhance the effect of PDT by avoiding direct contact with the tumor lesion, thus preventing its probe from contact re-exposure. Methods: We evaluated the efficacy of this irradiation technique for the lung cancer patients with endobronchial stenosis. Before the procedure, we evaluated the extent of tumor lesion by auto-fluorescence video-bronchoscope (BF TYPE-F260, Olympus, Japan). As a photosensitizer, talaporfin sodium (Lasershyrin, Meiji Pharma, Japan) was administrated at 40mg/m² intravenously 6 hours before irradiation. PDT was performed by using video-bronchoscope (ES-530T, FUJI MEDICAL, Japan) to visualize PD-laser light clearly by adjusting FICE (Flexible spectral Imaging Color Enhancement) mode. We irradiated 664nm laser light to the target bronchus with endobronchial stenosis utilizing an all-direction type laser probe covered with a GS (disposable K203 guide sheath kit, Olympus, Japan) at each dose of 100cm² (150mW) for 11 minutes and 7 seconds under fluoroscopic guidance. After one month, we evaluated the endoscopic efficacy of this method. Results: Between December 2014 and April 2015, we performed GS-PDT for three patients with pathologically diagnosed lung cancer, 1 squamous cell carcinoma, 1 adenocarcinoma and 1 small cell carcinoma. Stage IA squamous cell carcinoma patient with endobronchial stenosis underwent definitive therapy. Stage IA adenocarcinoma patient with endobronchial wall spread of tumor to proximal respiratory tract underwent a combination of induction chemotherapy-radiotherapy followed by sleeve left upper lobectomy as for definitive therapy to reduce the extent of lung resection. Stage IIIA limited-stage small cell lung cancer patient with the stenosis of right main and upper lobe bronchus underwent palliative therapy to improve oxygenation and to prevent obstructive pneumonia. One month after GS-PDT, we confirmed the endoscopic response (1 complete response, 2 partial response). No PDT-related complications occurred. Conclusion: New GS-PDT method was safe.
and could be an effective technique to accurately irradiate the lung cancer patients with endobronchial stenosis.

Keywords: Photodynamic therapy, Guide sheath, Lung cancer, Endobronchial stenosis

P1.04-006 SECOND PRIMARY LUNG CANCER: FIVE YEARS OF A SINGLE CENTER EXPERIENCE IN ITS DIAGNOSIS AND TREATMENT

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Background: Second primary lung cancer (SPLC) constitute an important dimension of the burden of cancer survivorship that needs to be taken into account when defining strategies for surveillance, prevention and counseling. In last three decades the incidence of SPLC in patients that had a history of a prior cancer out of the respiratory system is estimated 2-8%. Relative risks of SPLC may be smaller than previously reported may benefit from increased surveillance in this group of patients. The aim of this study was to evaluate the incidence, diagnosis, clinical behavior of patients with lung cancer were analyzed using Pearson Chi-Square. Results: SLC represents 2% of all lung cancers diagnosed during the period of study. The prior diagnosis of cancer for this patients was breast cancer in 46% of cases, cervix cancer in 40% of cases and the other diagnosis 14% of cases. All the patients have been under oncologic treatment with radio or chemotherapy. 20% of these patients have been smokers prior to first malignancy. The average age of the patients with SPLC was 55 years old. The ratio male to female was 1:10. The most frequent histotype found was adenocarcinoma in 60% of cases. The prior malignancy was diagnosed 5 years before the lung cancer. The average period of time from the diagnosis to the second malignancy was 3.7 years. 73% of cases with SPLC underwent an anatomic resection of the tumor. Conclusion: This study shows that patients with the prior risk for a SPLC are premenopausal women with breast cancer and cervical cancer. Changes in the prevalence of risk factors and diagnostic techniques may have affected more recent risks. The relative risk of developing SPLC in smokers is unclear. SPLC after oncologic treatment is an issue that raises many questions.

Keywords: second primary lung cancer

P1.04-007 Y STENTS IN MALIGNANT TUMOURS - LONG TIME FOLLOW UP AND SURVIVAL

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Background: Stent insertion is one of the standard methods of therapeutic bronchology. Stents can be applied to trachea or bronchi. Y stents are inserted to the tracheobronchial area around endobronchial bifurcation. The most frequent indications are the central malignant tumours, less frequently benign stenosis, phistulla or tracheomalatia. The prognosis of central stenosing bronchiectasis are running. The long term survival is supporting the idea of a careful follow up and shows advances in current oncological treatment.

Keywords: Photodynamic therapy, Guide sheath, Lung cancer, Endobronchial stenosis

P1.04-008 TUMOR PENTAPLICITY - CASE REPORT

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Background: Metachronous tumor multiplicity is a relatively common phenomenon, often related to mutagenic effects of some types of antitumor therapy. However, idiopathic tumor multiplicity is rare. We present the case report of a patient, who developed five different malignant tumors in fifteen years horizon (SPLC). Results: 56-year old patient was diagnosed renal cell carcinoma in year 2001 with subsequent nephrectomy. During follow-up, a coin lesion was recognized on chest x-ray, histologically and radiologically verified as stage IIA pulmonary adenocarcinoma. Patient underwent successful right lower lobectomy. In 2010 colorectal carcinoma was diagnosed followed by radio and chemotherapy. Prognosis is good in 2012. All these tumors were treated curatively. In 2014 a new mass appeared on chest x-ray. Repeated bronchoscopy failed to obtain valid histological sample. The positron emission tomography revealed malignancy suspicion and excluded the disseminated disease. Surgical resection was performed. Peroperative histology reported carcinoma of uncertain type and surgeon decided for completion of pneumonectomy. However, final histological report showed small-celled lung cancer (pT2aP2M2x). Despite adjuvant chemotherapy given the patient developed distant metastases and died subsequently due to tumor progression in February 2016. Conclusion: Tumor pentaplicity is a clinical situation with rare occurrence. Our patient didn’t receive chemotherapy until 2010 (adjuvant chemotherapy after radical colorectal carcinoma surgery), so there could be no influence of the first three malignancies therapy. We did not find tumor occurrence in the family, no external risk factor, the patient fits in none of defined hereditary cancer predisposition disorder. Detection of common driver mutations in all five tumors is running. The long term survival is supporting the idea of a careful follow up and shows advances in current oncological treatment.

Keywords: Photodynamic therapy, Guide sheath, Lung cancer, Endobronchial stenosis

P1.04-009 BACTERIAL POPULATION DYNAMICS IN COLONIZATION OF AIRWAY STENTS IN PATIENTS WITH CANCER

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Background: Stent placement is an increasingly used treatment for malignant tracheobronchial stenosis. The main complication related to airway stents is bacterial colonization causing chronic cough and sputum, halitosis, recurrent bronchial infections, pneumonia and even sepsis. The main objectives were to describe potentially pathogenic bacteria (PPM) involved in stent colonization and to analyze PPM dynamics during follow-up. Methods: Prospective study in patients with malignant stenosis treated with stent placement. Bronchial washings (BW) were performed before and at least 1 month after stent placement. Qualitative cultures of PPM isolated in BW were performed. Statistical analyses with R 3.2.3. Results: Total of 65 patients, 56 (86%) men, mean age 64 (±10) y/o, 58 (89%) current or former smokers, 2 (3%) bronchiectasis, 28 (43%) COPD. Cancers were: primary lung cancer (n=52, 80%) followed by thyroid (n=4, 6%), esophagus (n=2, 3%) and other (n=7, 11%), stenosis were located in trachea (n=14, 21%), main carina (n=16, 25%) and main bronchi (n=35, 54%), and stent types included metal (n=30, 46%) and silicone (n=35, 54%). Isolated PPM in BW (table 1). Airway colonization was absent in 14 (21.5%) and present in 79%, of which it was persistent in 33 (50.8%) and intermittent in 16 (24.6%). Only 2 (3.1%) became negative. Median time until colonization was 35 days (IQR 28-116), with no significant differences between
IN TURKEY CHARACTERISTICS OF LUNG CANCER AMONG ELDERLY PATIENTS

P1.04-011 DEMOGRAPHIC, CLINICAL AND SURVIVAL

P1.04-010 NEUTROPHIL TO LYMPHOCYTE, PLATELET TO LYMPHOCYTE RATIOS AND SYSTEMIC INFLAMMATION IN LUNG CANCER STAGES

Background: Lung cancer is associated with systemic inflammation which seems to influence the prognosis of the disease. Different affordable methods may be used to evaluate the systemic inflammation: erythrocyte sedimentation rate (ESR), Neutrophil to lymphocyte ratio (Ne/Ly), Platelet to lymphocyte ratio (Pl/Ly). The aim of the study is to assess the relation between TNM lung cancer stages and the systemic inflammation estimated by Ne/Ly, Pl/Ly and ESR. Methods: Patients with lung cancer were classified between TNM lung cancer stages and the systemic inflammation estimated to lymphocyte ratio (Pl/Ly). The aim of the study is to assess the relation sediments between TNM lung cancer stages and the systemic inflammation estimated by Ne/Ly, Pl/Ly and ESR. Methods: Patients with lung cancer were classified according to TNM lung cancer staging in two groups: Group A (I, II and IIIA) and Group B (IIIB, IV). A complete blood count (CBC) and ESR were determined. Ne/Ly and Pl/Ly ratios were calculated for all patients. The results were compared between the two groups. Results: 73 consecutive patients (22 in Group A and 51 in Group B) were analyzed. In Group A (16 males), the mean age was 63.73 ± 7.69 years, the median Ne/Ly: 4.46 (0.70-25.6), median Pl/Ly: 204.48 (3.88-651.25) and median ESR: 40 mm/h (3-120). In Group B (48 males), the mean age was 65.06 ± 10.09 years, the median Ne/Ly: 4.46 (0.70-25.6), median Pl/Ly: 204.48 (3.88-651.25) and median ESR: 40 mm/h (3-120). The values of Ne/Ly, Pl/Ly were significantly higher (p<0.009 respectively p=0.007) in Group B versus Group A, but no statistically significant difference was observed for ESR values. Conclusion: We found a relation between TNM lung cancer stages and the systemic inflammation assessed by neutrophil to lymphocyte (Ne/Ly) and platelet to lymphocyte (Pl/Ly) ratios. The values of Ne/Ly, Pl/Ly ratios were significantly higher in nonseparable stages (IIIB, IV). Erythrocyte sedimentation rate (ESR) seems not to be an appropriate method to evaluate this relation.

Keywords: lung cancer, systemic inflammation

IN TURKEY CHARACTERISTICS OF LUNG CANCER AMONG ELDERLY PATIENTS

P1.04-011 DEMOGRAPHIC, CLINICAL AND SURVIVAL CHARACTERISTICS OF LUNG CANCER AMONG ELDERLY PATIENTS IN TURKEY

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Background: To determine demographic, clinical and survival data of elderly lung cancer patients. Methods: We evaluated 2,637 patients with lung cancer between January 1990 and October 2010. Elderly patients were defined as those 65 years or older. The patients were classified into two groups: younger and older group. The demographic, clinical and survival data of the groups were compared. Results: 938 (37.6%) patients were in the older group and 1,639 (62.4%) were in the younger group. The female patients rate was 7.8% (p=0.238) and other cancer history (4.4% vs 3.3%; p=0.101), and family cancer history rate (p=0.664) were similar between two groups. Illiterate patients rate (20.1% vs 16.6%; p<0.001), occupational risks (9.2% vs 12.8%; p=0.055), current smoker and exsmoker rate (p=0.005), asbestosis exposure rate (p=0.005), COPD prevalence (15.1% vs 8.6%; p=0.001), and two or more comorbidity rate (21.1% vs 10.1%; p=0.001) of older group was higher than younger group. The symptom duration of the groups were 96.4 days and 92.8 days, respectively (p=0.359). Systemic complaints and extrapulmonary intrathoracic spread complaints of older group were higher than younger group (p=0.001 and p=0.025). Karnofsky performance status was lower in older group than younger group (79.3 vs 82.2; p<0.001). Radiological findings of asbestosis exposure was higher in the older group than younger group (6.9% vs 4.1%; p=0.002). There was no difference between the groups in terms of histology and stage (p=0.078 and p=0.254). The independent etiological risk factors of lung cancer in elderly patients were lower educational status, smoking, COPD and male gender by multivariable logistic regression analysis. The median survival was 8.0 ± 0.36 months (95% CI: 7.288-8.712) for older group and 9.0 ± 0.27 months (95% CI: 8.477-9.523) for younger group (log-Rank: 6.567; p=0.033). The factors affecting survival in the both groups stage, Karnofsky performance status and treatment by Cox regression analysis. Conclusion: These data indicate that lung cancer had different risk factors and short survival in elderly patients. These features should be considered in the management of these patients.

Keywords: elderly patients, lung cancer
Although the procedure can be performed under moderate sedation (MS) or general anesthesia through an artificial airway was not associated with an increased diagnostic yield, and therefore conscious sedation should be considered where appropriate, with general anesthesia reserved for those patients who are older, and with a higher perioperative risk. More research is needed to determine the impact of a positive diagnosis including physician pretest likelihood and PET/CT avidity are needed to improve diagnostic outcomes.

Keywords: EBUS-TBNA, moderate sedation, Diagnostic yield, lung cancer

P1.04-016 EBUS PLUS FLUOROSCOPY-GUIDED BIOPSY COMPARED TO CONSCIOUS SEDATION

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Background: Removal of endobronchial tumor is considered the first treatment of choice to improve respiratory status to dilate and maintain the airflow. In patients with inoperable tumors we frequently regard endoscopic treatment as the first treatment of choice, but the indications and decisions regarding the method require careful consideration. We reported the indications and efficacy of virtual navigated bronchial intervention for the treatment of bronchial tumors. To select safer and precisely approach for patients with bronchial tumors, we evaluate virtual navigated bronchial intervention using a high-speed 3-dimensional (3D) image analysis system, Synapse Vincent (Fuji Photo Film Co., Ltd., Tokyo, Japan). Methods: We set out to clarify, based on retrospective evaluation of routine work-up data in our charts and patient treatment data, the efficacy of virtual navigated bronchial intervention for the treatment of different types of bronchial tumors, yet representative of the spectrum of conditions we encounter, in order to provide a guide to techniques available in interventional bronchology for ablative lesions. All computed tomography (CT) must satisfy several conditions necessary to analyze images by Synapse Vincent. Synapse Vincent provides more information not only concerning tumor size and shape, but also whether the tumor invades surrounding tissue and the extent of airway and vessel involvement. Constructed images are displayed on a monitor, which can be utilized for deciding the simulation and interventional strategy and for navigation during interventional manipulation. Results: In these cases, Synapse Vincent was used to determine the best planning of virtual navigated bronchial intervention. The feasibility and safety of Synapse Vincent in performing useful preoperative simulation and navigation of interventional procedures lead to the safer, more precise, and less invasive for the patient, and easy to construct an image, depending on the purpose, in 5-10 minutes using Synapse Vincent. Moreover, if the lesion is in the parenchyma or sub-bronchial lumen, it helps to perform simulation with virtual skeletal subtraction to estimate potential lesion movement. By using virtual navigated system for simulation, bronchial intervention was performed with no complications safely and precisely. Conclusion: Preoperative simulation using virtual navigated bronchial intervention reduces the surgeon's stress level, particularly when highly skilled techniques are needed to operate on lesions. This task, including interventional simulation and navigation both pre- and during manipulation, can lead to greater treatment efficiency. These technological instruments should be helpful for bronchial intervention procedures, and are also excellent devices for educational training.

Keywords: Interventional bronchology, Virtual navigation system

P1.04-014 DIAGNOSTIC YIELD IN PATIENTS UNDERGOING EBUS-GBNA: A SINGLE CENTER EXPERIENCE

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Background: ALK positive advanced NSCLC patients could get significant benefit of targeted therapy. In Czech Republic, targeted therapy is payed as second- and more line treatment, required positive FISH result of ALK positive NSCLC tumour. Methods: We investigate ALK rearrangement in selected group of NSCLC patients starting from January 2011 via fluorescence in situ hybridization (FISH) with the Vyvis ALK Break Apart FISH Probe Kit (Abbott Molecular). We evaluate frequency of positive and inconclusive results. In the group of ALK positive patients we evaluate clinical behaviour of tumours and effectivity and side effects of ALK inhibitors. Results: From January 2011 till June 2016, 798 nonsquamous NSCLC tumour samples were evaluated by FISH method. 20 (3.2 %) of evaluated 660 samples were positive, 138 tumour samples were classified as ALK break inconclusive (17.3 %). ALK break positive group of patients consist of 13 men and 7 women, median age 68.5 years. 17 of them were adenocarcinomas, in two there were adenosquamous histology and in one NSCLC-NOS was found. The limit of ALK positivity was 10 % positive cells, the range of our positive results were 10 – 72 %.

6/20 patients were treated by crizotinib. Two of them received second ALK inhibitor ceritinib after failure of crizotinib, those patients are alive and well 5 and 8 years from diagnosis of adenocarcinoma st. IV. Three patients died before they could get an access to targeted therapy, seven others with low PS died before start of targeted therapy, in three others there is not actual need for targeted treatment. One patient on crizotinib died after 6 months of targeted treatment, two other died after one month of treatment, in one patient targeted therapy was refused due to intolerance. Conclusion: Patients suffering from advanced ALK rearranged NSCLC should have perspectives of long lasting tumour response on ALK inhibitors. ALK rearrangement in nonsquamous NSCLC tumours is not rare, management of side effects requires good cooperation with other disciplines, and are also excellent devices for educational training.

Keywords: NSCLC; ALK translocation; crizotinib; ceritinib
Keywords: endobronchial ultrasound, Lung biopsy, peripheral pulmonary lesion, fluoroscopy-guided

P01.04-017 THE SURVIVAL OF OUR PATIENTS DIAGNOSED WITH LUNG CANCER IN 2013
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Background: Lung cancer is an important health problem. To investigate the survival of our patients diagnosed in hospital with lung cancer and the situations that effect. Methods: Using the data processing an archive system of our hospital, patients were examined who had operated with C34 code in 2013. The rates of survival were calculated using Kaplan-Meier Method and compared with Long-rank method. The influence of age on survival was analysed with Cox’s proportional hazards regression model. For multivariate analysis Cox’s proportional hazards regression model also used. The level of p<0.05 accepted as significant. Results: 1563(83.5%) of 1871 patients were operated and compared with Long-rank method. The influence of age on survival was analysis Cox’s proportional hazards regression model also used. The level of p<0.05 accepted as significant. Results: 1563(83.5%) of 1871 patients were operated and compared with Long-rank method. The influence of age on survival was analysis Cox’s proportional hazards regression model also used. The level of p<0.05 accepted as significant. Results: 1563(83.5%) of 1871 patients were operated and compared with Long-rank method. The influence of age on survival was analysis Cox’s proportional hazards regression model also used. The level of p<0.05 accepted as significant. Results: 1563(83.5%) of 1871 patients were operated and compared with Long-rank method. The influence of age on survival was

Keywords: lung cancer, survey, effecting factors, surgery

P01.04-019 FINAL ANALYSIS OF LUNG MICROBIOME FROM PATIENTS UNDERGOING BRONCHOSCOPY
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Background: Recent studies have demonstrated diversity in the lung microbiomes of chronic obstructive pulmonary disease and healthy individuals. Lung microbial communities may not just serve as a predictor of cancer development, but also as a target of pharmacological cancer prevention strategies. We sought to characterize the lung microbiome diversity within patients with lung cancer for comparison to those with other cancers and those without cancer. Methods: Signed informed consent was obtained from patients ages ≥18 years undergoing a clinically indicated bronchoscopy. A bronchial lavage (BAL) was collected for research purposes after completing routine bronchoscopy procedures. Samples were prepped and DNA was extracted and sequenced using 16S rRNA primers used to amplify Variable Region 4. Amplicons were sequenced and grouped into 100% operational taxonomic units (OTUs) using vsearch. Taxonomy was assigned, a phylogenetic tree was constructed, and sequences aligned for phylogenetic

Keywords: lung cancer, survey, effecting factors, surgery

P01.04-018 OCCURRENCE OF TRIPLE MULTIPLE MALIGNANCIES WITH LAST LUNG SQUAMOUS CELL CARCINOMA - CASE REPORTS
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Background: The incidence of multiple primary tumours (MMPNs) ranges from 0.73 to 11.7%. Most often occur double malignancies - 3-5%, much less triples - 0.5%. The aim of the study is to describe the three cases of triple metachronous multiple malignancies, the last of which was a squamous cell carcinoma of lung in all three patients. Methods: A retrospective analysis of all medical histories (1763) patients who were hospitalized in the Pulmonary Hospital Hospital in Olsztyn, Poland in the period from January 2013 to October 2015, with a diagnosis of at least one neoplasms was performed. We selected only those patients who were diagnosed with histologically confirmed three independent malignancies. Results: The incidence of tumours of triple malignancies was 0.52%. Of all cases of triple malignancies, we selected 3 cases - 2 men and 1 woman, whose last growing cancer, histopathologically confirmed, was squamous cell lung cancer. Case No. 1 - 54-year-old man with COPD (GOLD 2), who gave up smoking, melanoma of the scalp treated surgically and by chemotherapy (6xDTIC) at the age of 19, Hodgkin NS II at the age of 38 treated with 6xABVD, at the age of 53 years diagnosed with squamous cell carcinoma of the left lung in stage T2N1M0. Due to the low value of spierometry disqualified from surgery, qualified for radiotherapy. Case No. 2 - 67-year-old man with a history of hypertension, colon cancer at the age of 56, after a large resection of polyp and laryngeal squamous cell carcinoma at the age of 63, diagnosed with asymptomatic squamous cell carcinoma of the right lung in a stage T2NOM0 at the age of 65. Case No. 374-year-old woman with atrial fibrillation, stable ischemic heart disease, tongue cancer at the age of 67, and its recurrence in the age of 72, after a right-sided mastectomy and chemotherapy for breast cancer at the age of 69, at the age of 74 diagnosed with squamous cell carcinoma of the left lung. The average age of first cancer was 47, the second 57 years, the third 64 years. Conclusion: 1. Lung cancer often occurs as a subsequent malignancy 2. Another primary malignant may develop even 30 years later, and therefore the possibility of development the third or another cancer should be considered for all cancer patients. 3. Development of synchronous or metachronous neoplasms should be considered in any case in patients with previous oncological treatment. Keywords: case report, triple metachronous multiple malignancies, multiple malignancies, Squamous cell lung cancer

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Background: Medical thoracoscopy is a minimally invasive procedure utilized mainly by pulmonologists for the diagnosis and management of pleural effusions. The aim of this study was to evaluate the efficacy and safety of medical thoracoscopy when performed by a combined team of pulmonologists and thoracic surgeons in a tertiary university hospital. Methods: This is a retrospective cohort analysis of all patients with pleural effusion who underwent medical thoracoscopy at “LAIKO” Athens General Hospital from June 2013 to December 2014. Results: Our study population included 36 patients, 18 males and 18 females, with a mean age of 61 years. All patients were submitted to medical thoracoscopy for the diagnostic evaluation of pleural effusion. Twenty-six patients (26/36, 72.2%) presented with an undiagnosed pleural effusion, six (16.7%) with known malignant, recurrent pleural effusion, three (8.3%) with parapneumonic effusion/empyema and one (2.8%) with idiopathic pleural effusion due to nephritic syndrome. Eighteen patients (18/36, 50%) underwent drainage and pleural biopsy, 9 patients (9/36, 25%) underwent drainage, pleural biopsy and talc pleurodesis, 6 patients (6/36, 16.7%) underwent drainage and talc pleurodesis due to known malignant pleural effusion and 3 patients (3/36, 8.3%) underwent drainage of their parapneumonic effusion/empyema. Among all patients (n=27) who underwent diagnostic pleural biopsy, 2 patients (7.4%) were diagnosed with primary non-small cell lung cancer, 4 with malignant pleural mesothelioma, 3 (11.1%) with metastatic disease of non-thoracic primary origin and 3 (11.1%) with lymphoma, while 1 patient each (3.7%) was diagnosed with tuberculosis, systemic lupus erythematosus, chronic inflammation, chronic pleural fibrosis and nephritic syndrome. In 3 patients (3/36, 8.3%) the biopsy was negative. Medical thoracoscopy was non-diagnostic in one patient only (1/27, 3.7%), thus producing a diagnostic yield of 97.3%. With the notable exception of one patient (1/36, 2.8%) who died due to empyema and subsequent sepsis, the remaining post procedural complications were mild, and included subcutaneous emphysema in 6 cases (6/36, 16.7%) and minor bleeding in 3 cases (3/36, 8.3%). Conclusion: When performed by a combined team of pulmonologists and thoracic surgeons in a tertiary level hospital, medical thoracoscopy is a relatively safe and efficacious technique for the diagnosis and management of pleural effusions in patients unable to undergo or not requiring surgical intervention.

Keywords: medical thoracoscopy, pleural effusion, pleural biopsy, pulmonologists
Abstracts

POSTER SESSION 1 - P1.04: PULMONOLOGY – MONDAY, DECEMBER 5, 2016

P1.04-023 THROMBOMODULIN INHIBITS THE GROWTH AND ANGIogenesis OF HUMAN LUNG CANCER VIA BLOCKING VEGFR2-MEDIATED JAK/STAT3 SIGNALING PATHWAY
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Background: Angiogenesis has been an attractive target for drug therapy because of its key role in the growth and metastatic spread of malignant tumor. Thrombomodulin has been shown to possess anti-inflammatory and vascular endothelial protection activities. However, its roles in tumor angiogenesis are unknown. The aim of this study was to investigate the roles of thrombomodulin in tumor angiogenesis and its anticaner activities.

Methods: ex vivo aortic ring angiogenesis sprouting assay was used to detect its neo-vascularization. Western blotting was performed to examine STAT3 signaling cascade. Results: Thrombomodulin significantly inhibited human umbilical vascular endothelial cell (HUVEC) proliferation, migration and tube formation in vitro and blocked vascular endothelial growth factor (VEGF)-triggered angiogenesis in vivo.

Discussion: VEGF receptor (VEGFR) 2 mediated-JAK/STAT3 signaling pathway was significantly inhibited by thrombomodulin in endothelial cells. In addition, the constitutively activated STAT3 protein, and the expression of STAT3-dependent target genes, thrombomodulin in tumor angiogenesis and its anticancer activities.

POSTER SESSION 1 - P1.04: PULMONOLOGY – MONDAY, DECEMBER 5, 2016

P1.04-025 THE IMPACT OF EMERGENCY PRESENTATION ON SURVIVAL OF LUNG CANCER PATIENTS
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Background: A significant proportion of lung cancer patients are diagnosed through emergency department (ED), which is usually associated with poorer prognosis. We investigated the association between diagnosis of lung cancer after presentation through emergency department due to symptoms associated to lung cancer.

Methods: Medical charts of patients with lung cancer patients newly diagnosed in Department for Respiratory Diseases Jordanovac, University Centre Zagreb in years 2012 and 2013 were reviewed. Overall survival was calculated and was compared between groups. Results: The medical charts of 951 males and 407 females, mean age 64 years (males 64.5, females 62) were reviewed. Males were diagnosed with lung cancer after initial presentation through ED. The most common reasons for ED admissions were hemoptysis (in 31% of patients), pneumonia (19%), brain metastasis (15%), dyspnea (10%) and superior vena cava syndrome in 8% of patients. There were no differences in histology subtypes between two different routes of presentation (comparison of primary histologic subtype was adenocarcinoma followed by squamous histology).

Significantly higher proportion of patients diagnosed after initial diagnosis through ED were at presentation in stage IV (61 vs 44%, p<0.0001), poorer performance status (ECOG 3 vs ECOG 0, p<0.0001), significantly less patients underwent surgical resection (18% vs 5%, p<0.0001) and radiotherapy (56 vs 73%, p<0.0001). Median overall survival (mOS) was significantly lower in patients diagnosed through ED (6.0 vs 10.0 months, p<0.0001). In patients with non-small cell lung cancer (NSCLC) results were similar (mOS 6.0 vs 10.0 months, p<0.0001). In patients with small cell lung cancer (SCLC) mOS was also significantly worse (7.0 vs 9.0 months, p<0.0001) in patients diagnosed through ED. Conclusion: Higher stage, reduced access to surgical resection and radiotherapy, and significantly lower overall survival regardless of histology subtypes among lung cancer patients who present through emergency department, stress out the importance of earlier diagnosis of lung cancer patients so that initial presentation through emergency department can be reduced.

P1.04-024 MOLECULAR PROFILING AND SURVIVAL OF PRIMARY PULMONARY NEUROENDOCRINE CARCINOMA WITH COMPLETELY RESECTION
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Background: According to the 2015 World Health Organization classification of lung tumors, pulmonary Large cell neuroendocrine carcinoma (PLCNC) is grouped with the small cell lung cancer (SCLC) and carcinoid as pulmonary neuroendocrine carcinoma (PNC) for the common features of neuroendocrine characteristics. Molecular profiles and prognosis of primary pulmonary neuroendocrine carcinoma (PNC) are not well investigated currently. We conducted present study to evaluate genomic abnormality and survival differences in patients with primary PNC. Methods: Tumor samples of PNC after completely resection from Zhejiang Cancer Hospital were collected from 2008 to 2015. Nine driver genes including six mutation (EGFR, KRAS, NRAS, PIK3CA, BRAF, HER2) and three fusions (ALK, ROS1, RET) were examined by RT-PCR. Survival analysis was evaluated using the Kaplan-Meier method.

Results: Totally, 108 patients with pathologic confirmed PNC were enrolled. Samples included 52 PLCNC, 44 small cell lung cancer (SCLC) and 12 carcinoid. Twelve patients were found to harbor genomic abnormalities (11.1%). The most frequent gene abnormality was PIK3CA (n=5, 5.6%), followed by EGFR (n=3, 2.8%), KRAS (n=2, 1.9%), ALK (n=1, 0.9%), RET (n=1, 0.9%). No ROS1, BRAF, NRAS and HER2 mutations were observed. The frequencies of gene aberrations in PLCNC, SCLC, and carcinoids were 15.4%, 8% and 8.3%, respectively. Sixty-seven patients were with recurrence or metastasis after surgery, including 32 PLCNC, 33 of SCLC, and two of carcinoid (both were atypical carcinoid). Among the 32 patients with PLCNC, none received molecular targeted treatment, 28 received first-line chemotherapy, including 18 of etoposide/platinum regimen and 10 of other platinum-based treatment. The progression free survival in patients with etoposide/platinum regimen was longer than patients with non-etoposide/platinum treatment (4.8 vs 3.4 months, P=0.019). Survival difference was observed among the PLCNC, SCLC and carcinoid group (37.0 vs 34.0 vs not reached, P=0.035), but no difference existed between the PLCNC and SCLC group (P=0.606). Conclusion: Common genomic abnormality is rare in PNC patients and most frequently observed in PLCNC. Patients with carcinoid had a superior survival than PLCNC and SCLC.

Keywords: large cell neuroendocrine carcinoma, pulmonary neuroendocrine carcinoma, genomic aberration

POSTER SESSION 1 - P1.04: PULMONOLOGY – MONDAY, DECEMBER 5, 2016

P1.04-026 COEXISTING LUNG CANCER AND INTERSTITIAL LUNG DISEASE: A CHALLENGE IN CLINICAL PRACTICE
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Background: Lung cancer (LC) risk is increased in patients with interstitial lung disease (ILD), and the two diseases sometimes occur concomitantly. Cigarette smoking is a recognised risk factor for development of both pathologies but the aetiology and pathogenesis of LC in patients with ILD is still unclear. The benefit of chemotherapy or radiotherapy for LC in cases of LC and ILD is unknown. Objective: To explore the characteristics and outcomes of patients with ILD and LC. Methods: A retrospective analysis of all patients presenting with concomitant ILD and lung cancer to our centre, between 1st January 2011 and 30th June 2016, was performed. Diagnosed lung cancer patients with suspected ILD, but not confirmed, were excluded, as well as patients who developed ILD in the setting of lung cancer therapy. Clinical, radiological and pathological characteristics of this cohort were described. Outcomes were also reported. Results: Eleven patients were included (mean age 63±12years). Most patients were men (82%) and heavy smokers (64%) had a smoking history >30pack/year. The majority ILD cases were related to connective tissue disease (65%) and combined pulmonary fibrosis and emphysema (CPFE) (18%). The most prevalent lung cancer histological type was adenocarcinoma (45%); most patients were diagnosed at advanced stages (63%) and mainly during the clinical and radiological follow-up for
the fibrosis. The mean time from the onset of ILD to the onset of LC was 39.4 months. On chest CT, the tumours were predominantly peripheral. Surgical resection was performed in 3 patients with stage I or II LC, chemotherapy and/or radiotherapy were given to 5 patients with advanced disease (stage III and IV). One patient was refused for radiotherapy due to considerations of the adverse effects on the prognosis. The median survival since the diagnosis of LC was 6.7 months. Two patients died of respiratory failure due to progression of pneumonitis after the therapy and three patients died due to progression of LC. Conclusion: Patients with LC and ILD might benefit from chemotheraphy and radiotherapy, but pre-existing ILD could influence negatively the prognosis. Therapy for LC should be considered in patients presenting both LC and ILD and interdisciplinary evaluation of therapeutic options is mandatory. When planning radiotherapy it is important determine the radiation pneumonitis risk. More studies are needed to clarify the role of LC treatment in the management of ILD patients.

Keywords: lung cancer, interstitial lung disease, lung cancer treatment, outcomes

Background: Surgery is considered the first line treatment for patients with resectable early non-small cell lung cancer (NSCLC). Many of these patients present limited lung function which is caused by a common etiologic factor - cigarette smoking. The evaluation of pulmonary function preoperatively is important to identify candidates at risk of postoperative respiratory complications and may assist in operability decision. However, lung function after surgical resection may be affected by several factors. Objective: To evaluate changes in pulmonary function after thoracic surgery, in patients with solitary nodules or lung cancer. Methods: Retrospective study of patients diagnosed with operable lung cancer and solitary nodules followed in our centre between 1st January 2011 and 31st December 2014. Patients presenting pulmonary function tests (PFTs) until one year after surgery were included. Patients without PFTs after surgery were excluded. Results: Forty three patients were included. The results are presented in the table:

| Mean age | 62±9 years |
| Gender | 67.4% (n=29) male |
| Indications for surgery | Adenocarcinoma 44.2% (n=19) 14% (n=6) 11.6% (n=5) 25.6% (n=11) |
| Solitary pulmonary nodule | 44.2% (n=19) 14% (n=6) 11.6% (n=5) 25.6% (n=11) |
| Clinical staging in lung cancer patients IA IIIA | 43.7% (n=14) 15.6% (n=6) 12.5% (n=4) 18% (n=7) |
| Location of the lesion | Superior right lobe 36.4% (n=15) 25.6% (n=11) |
| Neoadjuvant chemotherapy Neoadjuvant radiotherapy | 20.9% (n=9) 4.7% (n=2) |
| Open surgery Video-assisted thoracic surgery (VATS) | 83.7% (n=36) 16.3% (n=7) |
| Comorbidities | Chronic Obstructive Pulmonary Disease (COPD) Ischemic Heart Disease (IHD) 30.3% (n=13) 4.7% (n=2) |
| Smoking habits | Smoker Ex-smoker Non-smoker 37.2% (n=16) 32.6% (n=14) 30.2% (n=13) |

The mean values of FVC (L), FEVI (L), FEVF/V and DLCO decreased after surgery (p=0.010, p=0.001, p=0.011 and p=0.037, respectively). FVC (L) and FVC (%) values decreased more significantly in patients submitted to pneumonectomy (p=0.004 and p=0.047). There was, though, an improvement of FVC (L) in patients submitted to VATS and wedge resection (p=0.005 and p=0.034). FEVI (L) mean values increased in patients submitted to wedge resection (p=0.017) and decreased in patients submitted to pneumonectomy (p=0.04). There was no significant association between histological type, clinical stage, local of the lesion, COPD and CYD and lung function parameters before and after surgery. Conclusion: The postoperative pulmonary function varied according to the type of surgery, therefore the surgical procedure adopted may help us predict changes in lung function after lung surgery. Clinicians should be aware of these changes when determining the surgical method, especially in high risk patients.

Keywords: lung cancer, Thoracic Surgery, pulmonary function test, outcomes

Background: PROMs - including symptoms, health related quality of life, well-being and functional status - are commonly measured in clinical trials. They are used in a variety of ways, including therapy decisions on individual patient level or research into disease progression. Optimizing how patients feel is a good goal of oncology practice and a quality performance indicator of care. Therefore it is important to implement the collection of PROMs during routine lung cancer treatment without disturbing the routine workflow. The International Collaboration in Health Outcomes Measurement (ICHOM) has proposed a standard set of uniform PROMs for lung cancer (Mak et al, ERJ 2016). Methods: A pilot study is set up to establish an operational workflow and to identify trouble shooting to the collection of PROMs in standard of care. Self-reporting by the patient is conducted via a web-based interface using questionnaires adapted to the ICHOM standard set according to the ICHOM standard set.

Keywords: Pilot, PROM, ICHOM

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Keywords: lung cancer, Thoracic Surgery, pulmonary function test, outcomes
prognostic for lung squamous cell carcinoma (SCC) under a NCI/SPECS (Strategic Partnerships fo Evaluating Cancer Signatures) award. The study design specifies a primary validation cohort comprising institutional cases, and an additional validation cohort of Cooperative Group cases, all profiled via a common pipeline. Methods: Completely resected SCC (confirmed by central pathology review) meeting clinical (Stage I-II; complete 3-year follow-up) and specimen quality criteria (Tumor cellularity ≥ 50%; necrosis ≤ 20%) were submitted by 6 institutions. Clinical, pathological and outcome data were uploaded to a central database. Lyrates from 5 um sections of FFPE SCC tumor samples were run on the HTG EdgeSeq Processor (HTG Molecular Diagnostics, Tucson, AZ) using the mRNA whole transcriptome assay in which an excess of nuclear protection probes (NPPs) complimentary to each mRNA hybridizing to their target. SI nuclease then removes un-hybridized probes and RNA leaving behind only NPPs hybridized to their targets in a 1:1 to 1 ratio. Samples were individually barcoded (using a 16-cycle PCR reaction to add adapters and molecular barcodes), individually purified using AMPure XP beads (Beckman Coulter, Brea, CA) and quantitated using a KAPA Library Quantification kit (KAPA Biosystems, Wilmington, MA). Libraries were sequenced on the Illumina HiSeq platform (Illumina, San Diego, CA) for quantification. Standardization and normalization was provided to the project statistical core for validation of two pre-existing signatures and generation of new models (MCP clustering). Results: Among 224 cases with mRNA data, median age was 70 (43-92), 143 (64%) male, with 67% former (87%) and current (26%) smokers. All patients were completely resected stage I or II. At follow-up, 59 (26%) had documented recurrence and 129 (58%) were deceased. To date, we have been unable to validate the previous models, but have created a novel signature of three miRNAs (see Figure) that is being validated in the second phase of the project using an independent, blinded multi-institutional cohort. Conclusion: The Squamous Lung Cancer SPECS Consortium has established well-annotated and quality-controlled resources for validation of prognostic miRNA signatures. A new candidate 3-miRNA signature has been identified for further development as a clinically useful biomarker.

Keywords: Squamous cell lung cancer, gene expression signature

POSTER SESSION 1: P1.05: EARLY STAGE NSCLC TRANSLATIONAL RESEARCH & BIOMARKERS – MONDAY, DECEMBER 5, 2016

P1.05-002 THE PROGNOSTIC IMPACT OF EGFR MUTATION STATUS AND MUTATION SUBTYPES IN PATIENTS WITH SURGICALLY RESECTED LUNG ADENOCARCINOMAS

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Background: EGFR mutation status is a well-established predictor of the efficacy of EGFR tyrosine kinase inhibitors (TKIs) in non-small cell lung cancer. Recently, the differences in EGFR mutation subtypes were also reported to be associated with the efficacy of EGFR TKIs. However, the prognostic impact of EGFR mutation status and mutation subtypes remains controversial. Methods: We retrospectively reviewed 945 consecutive patients with surgically resected adenocarcinomas who had their EGFR mutation status analyzed between January 2010 and December 2014. Overall survival (OS) and recurrence-free survival (RFS) were analyzed in all patients, pathological stage I patients, and patients with exon 21L858R point mutation or exon 19 deletions) using Kaplan-Meier methods and Cox regression models. Results: The median follow-up time was 42 months. The results for EGFR mutation status, mutation subtype, and the comparison data of OS/RFS are summarized in the attached Table. Positive EGFR mutation status was significantly associated with longer OS/RFS in all patients and was also associated with longer OS in pathological stage I patients. However, no significant differences were observed in OS/RFS between patients with exon 21L858R point mutation and those with exon 19 deletions. In a Cox regression model for OS, the EGFR mutation status was a significant prognostic factor that was independent of well-established prognostic factors such as age, pathological stage, vascular invasion, lymphatic permeation, and serum CEA level.

Keywords: EGFR mutation status, prognosis

Conclusion: Positive EGFR mutation status is a favorable prognostic factor in patients with surgically resected lung adenocarcinomas. However, EGFR mutation subtypes (exon 21L858R point mutation or exon 19 deletions) have no prognostic impact.

Keywords: prognostic factor, EGFR, lung adenocarcinoma

POSTER SESSION 1: P1.05: EARLY STAGE NSCLC TRANSLATIONAL RESEARCH & BIOMARKERS – MONDAY, DECEMBER 5, 2016

P1.05-003 CO-EXPRESSION OF CD274 AND PD-L1 FREQUENTLY OBSERVED IN RESECTED NSCLC TUMORS FROM SMOKERS

Aaron Lieder,1 Robert McKenna,2 Judy Derig,1 Hsiao-Wang Chen,2, Naimeh Kamarnpou,1 Dongmei Hou,1 Maria Velez,2 Robert Cameron,1 Jay Lee,3 Steven Dubinett,1 Dennis Slamon2
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Background: With the approval of anti-programmed cell death-1 (PD-1) therapy in advanced non-small cell lung cancer (NSCLC), identifying patients with early stage disease most likely to benefit from therapy has become a priority. It has been hypothesized that patients whose tumors show evidence of PD-1 mediated T cell exhaustion, via the presence of both tumor infiltrating lymphocytes (TILs) and PD-L1 expression, are more likely to respond to anti-PD-1 therapy (Teng et al, 2015). The current study utilized microarray analysis to evaluate the relationship between both clinicopathologic features and overall survival (OS) with tumor microenvironment (TME) composition. Methods: Gene expression microarray analysis was performed using the Agilent Whole Human Genome 4x44K 2-color platform for 319 NSCLC and 15 normal resection specimens. The reference sample was an equal mixture of 258 of the NSCLC samples. Rosetta Resolver and Statistica 13.0 were used for analysis. Samples with PD-L1 expression levels greater or unchanged from reference level were classified as positive, while those significantly lower (log (ratio)<0 and p<0.01) than the reference were classified as negative. CD8a expression was used as a surrogate for TILs as previously described by Ock et al. (2016), and categorized in the same manner as PD-L1. Relationships between TME composition and clinicopathologic features were evaluated with the chi-square test. Survival analysis was performed using the Kaplan-Meier method and compared using the log-rank test. Results: In the 319 NSCLC samples the incidence of a Type I TME (+CD8a/+PD-L1) was 45%, Type II TME (-CD8a/-PD-L1) 12%, Type III (CD8a/+PD-L1) 25%, and Type IV (+CD8a/-PD-L1) 18%. When assessing for survival, patients with a PD-L1 negative/CD8a negative (Type IV) TME had improved OS compared to patients with PD-L1 negative/CD8a negative (Type II) TME (p=0.02). When assessed for smoking, ever smokers were more likely to evidence a PD-L1 positive/CD8a positive (type I) TME compared to never smokers, 49% vs 32%, while never smokers more frequently evidenced a PD-L1 positive/CD8a negative (Type III) TME compared to ever smokers, 37% vs 22% (P<0.05). Interestingly, 75% of normal lung samples evidenced a PD-L1 positive/CD8a positive microenvironment. Conclusion: Evidence of both TILs and PD-L1 expression was observed in the majority of normal lung specimens and also more frequently in tumors from smokers compared to non-smokers. Patients whose tumors showed evidence of CD8a, but not PD-L1, had improved OS compared to patients without evidence of either. Future studies will utilize immunohistochemistry to corroborate these findings and investigate other components of the TME.

Keywords: Immunotherapy, PD-L1, Tumor Infiltrating Lymphocytes (TILs), tumor microenvironment

POSTER SESSION 1: P1.05: EARLY STAGE NSCLC TRANSLATIONAL RESEARCH & BIOMARKERS – MONDAY, DECEMBER 5, 2016

P1.05-004 SURFACTANT PROTEIN C IS A PROGNOSTIC MARKER IN RESECTED NON-SMALL CELL LUNG CANCER

All Pts 3y-RFS 5y-RFS P 3y-OS 5y-OS P
All Pts 0.009 < 0.001

EGFR mut+ (N = 423) 84.6% 76.7% 95.2% 89.0%

EGFR mut- (N = 522) 78.8% 71.2% 84.9% 76.5%
p stage I Pts 0.102 < 0.001

EGFR mut+ (N = 352) 93.4% 85.4% 98.2% 94.5%

Conclusion: Positive EGFR mutation status is a favorable prognostic factor in patients with surgically resected lung adenocarcinomas. However, EGFR mutation subtypes (exon 21L858R point mutation or exon 19 deletions) have no prognostic impact.

Keywords: prognostic factor, EGFR, lung adenocarcinoma

EGFR mutation status, OS/RFS
Background: The lung cancer cells express genes involved in key points of the lung development. The objective of this study was to determine the prognostic value of embryonic markers in tumour tissue samples from patients with surgically-treated non-small cell lung cancer (NSCLC). Methods: Study based on 129 primary tumour samples from 102 patients with surgically-treated NSCLC (99% R0) and 27 lung samples. Expression of the following markers was evaluated by mRNA RT-qPCR assay: CEACAMS, FGFR2b, FRS2, MYCN, SFTPC, SHH, SHP2, and SOX17 in the tumour and lung samples. Statistical analyses included chi-squared tests, non-parametric tests, Kaplan Meier curves, log-rank and Cox regression tests. Results: Patients' characteristics were: mean age 67 ± 8 years, squamous carcinoma (49%), adenocarcinoma (43%), pathological staging: I: 56%, II: 32%, III: 11% and IV: 1%. 18% received adjuvant chemotherapy. Kaplan-Meier curves of SFTPC were plotted in figure 1. Underexpression of SFTPC in tumour samples related to lung samples (p<0.05). FGFR2b showed similar expression and FRS2, SFTPC, SHH, SHP2 and SOX17 were underexpressed (p<0.05). The squamous carcinomas expressed more FGFR2b, FRS2 and SFTPC (p<0.05), while adenocarcinomas expressed more CEACAM5 (p>0.05). The squamous carcinomas expressed more FGFR2b, FRS2 and SFTPC (p<0.05), while adenocarcinomas expressed more CEACAM5 (p>0.05). The squamous carcinomas expressed more FGFR2b, FRS2 and SFTPC (p<0.05), while adenocarcinomas expressed more CEACAM5 (p>0.05). The squamous carcinomas expressed more FGFR2b, FRS2 and SFTPC (p<0.05), while adenocarcinomas expressed more CEACAM5 (p>0.05). The squamous carcinomas expressed more FGFR2b, FRS2 and SFTPC (p<0.05), while adenocarcinomas expressed more CEACAM5 (p>0.05)

Conclusion: Underexpression of SFTPC in tumour samples was independently associated with worse prognosis.

Keywords: Surgery, prognostic marker, lung development, non-small cell lung cancer
Abstracts

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POSTER SESSION 1: P1.05 - EARLY STAGE NSCLC
TRANSLATIONAL RESEARCH & BIOMARKERS – MONDAY, DECEMBER 5, 2016

P1.05-007 ANALYSIS OF RNA SEQUENCING DATA ALONG WITH PET SUV-MAX CAN DISCOVER NOVEL GENE SETS WHICH CAN PREDICT SURGICAL OUTCOME OF NSCLC
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Background: Recent development of NGS technology provides a better understanding on the molecular mechanism of the cancer. A comprehensive analysis algorithm of NGS data along with various clinical phenotypes and clinical outcome may lead discovery of novel molecular mechanism of cancer biology. It has been suggested that the preoperative SUV of the PET-CT is related to the aggressiveness of the cancer. We hypothesized that the identification of genes that were related to the PET SUV-max would lead a discovery of novel genes which could predict long-term outcomes of patients of non-small cell lung cancer. Methods: We set a 51 adenocarcinoma and a 101 squamous cell carcinoma patients cohort, whose cancer and normal tissue samples were presented with CummeRbund R-package. Results: Based on the analysis algorism of NGS data along with various clinical phenotypes and understanding on the molecular mechanism of the cancer. A comprehensive analysis algorithm of NGS data along with various clinical phenotypes and clinical outcome may lead discovery of novel molecular mechanisms, which can be used to improve the molecular classification of NSCLC.

Keywords: mRNA, patient-derived xenografts, miRNA, Prognosis

Conclusion: Our results suggest that it is necessary to set a comprehensive analysis algorithm of the NGS data along with various clinical phenotypes of the patients, for the discovery of clinically meaningful molecular mechanisms of the cancer.

Keywords: NSCLC, transcriptome, NGS, recurrence

POSTER SESSION 1: P1.05 - EARLY STAGE NSCLC
TRANSLATIONAL RESEARCH & BIOMARKERS – MONDAY, DECEMBER 5, 2016

P1.05-008 DETECTION OF EGFR MUTATIONS IN PULMONARY VEIN AND PERIPHERAL BLOOD PLASMA CELL-FREE DNA FOR ANALYSIS OF SURGICAL TREATMENT IN EARLY-STAGE NSCLC
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Background: Free circulating DNA (cfDNA) has been known for several decades. These small DNA fragments are released into the circulation from nucleated cells through necrosis, apoptosis and/or active secretion. Use of blood plasma cfDNA to detect mutations has spread widely as a form of liquid biopsy. However, it remains unclear which types of samples are appropriate for detecting tumor cell-free DNA in these biopsies. We compared the abundance of EGFR mutations in peripheral blood and pulmonary vein plasma cell-free DNA from patients with early-stage NSCLC. Methods: In this study, primary lung tumors and matched presurgery peripheral blood plasma samples and intraoperative pulmonary vein blood samples were collected from patients with early-stage NSCLC (n=89). We detected EGFR mutations (exon19 deletion, L858R, G719X, S768I and T790M) in 89 early-stage lung cancer samples using droplet digital PCR (ddPCR) and amplification refractory mutation system (ARMS). EGFR mutation abundance was determined and analyzed to reveal potential impact of samples types. Results: Presurgery peripheral blood plasma samples (n=89) and intraoperative pulmonary vein blood samples (n=89) matched tumor tissue samples (n=89) were analyzed for EGFR mutations using ddPCR and ARMS respectively. Of the 41 EGFR mutations detected in tumor tissues by ARMS, 37 of the corresponding mutations were detected in presurgical peripheral blood plasma cfDNA and intraoperative pulmonary vein cfDNA, whereas 6 mutations were found in plasma from patients with EGFR wild-type tumors (sensitivity 80.49%, specificity 91.67%). Free circulating DNA was identified in the plasma of pulmonary venous blood and peripheral blood in thirty-seven patients. Of the 37 cases of EGFR mutation positive plasma samples, ddPCR identified a higher mutation abundance of pulmonary venous samples than peripheral blood (1.05% vs. 0.12%, p = 0.007). Conclusion: This study demonstrates accurate mutation detection in plasma using ddPCR, and that cfDNA can be detected in presurgical peripheral blood and intraoperative pulmonary vein in patients with early-stage lung cancer. Our results suggest that pulmonary venous blood can be obtained from the resected specimen, thus facilitating the detection of cfDNA. Future studies can now address whether monitoring the change of EGFR mutation abundance after surgery identifies patients at risk for recurrence, which could guide therapy decisions for individual NSCLC patients.

Keywords: plasma, pulmonary vein, lung cancer, cell-free DNA

Conclusion: Our results suggest that it is necessary to set a comprehensive analysis algorithm of the NGS data along with various clinical phenotypes of the patients, for the discovery of clinically meaningful molecular mechanisms of the cancer.

Keywords: NSCLC, transcriptome, NGS, recurrence
Compared with traditional tumor marker, CTC detection could provide more significant meaning in the differential diagnosis of SPN. The positive and negative predictive value (PPV and NPV) in differential diagnosis of SPN for SPN with different size. For SPN with diameter less than 8 mm, the PPV and NPV of CTC were 89% and 74%. Then the patients were divided into three groups according to the nodule diameter to evaluate the diagnostic value of CTC in differential diagnosis of SPN for patients' prognoses in a relatively large cohort. Methods: We assessed TFF-1 gene copy number and protein expression in microarrayed 636 NSCLC, including 421 adenocarcinomas and 173 squamous cell carcinomas (SCCs), and 42 other histologies, using fluorescent in situ hybridization and immunohistochemistry. TFF-1 copy number alterations were divided into three categories: amplification (TFF-1/CEP14 > 2), polysomy (TFF-1/CEP14 > 2 and TFF-1 signals > 4 copies per nucleus), and disomy (the others). Their associations with clinical data were retrospectively analyzed. Results: Among the entire cohort, TFF-1 amplification and polysomy were observed in 5.6% (36/636) and 8.3% (53/636), respectively. Tumors with copy number alterations (amplification and polysomy) were detected in 14.5% (91/624) among adenocarcinomas, 9.3% (17/173) among squamous cell carcinomas, and 26.2% (11/42) among other histologies (P = 0.012). TFF-1 expression was almost exclusively observed in adenocarcinomas (P < 0.001). In the adenocarcinoma cohort, the frequency was 6.7% (28/421) for TFF-1 amplification and 7.8% (33/421) for polysomy. TFF-1 positivity was 34.8% (357/1021). A multivariate Cox hazards model analysis demonstrated that TFF-1 amplification was an independent worse prognostic factor (hazard ratio (HR), 3.84; 95% confidence interval (CI), 2.18-6.71) for overall survival, but TFF-1 expression was adversely an independent better prognostic factor (HR, 0.69; 95% CI, 0.29-0.85). In the SCC cohort, there were few cases of TFF-1 amplification (1.7%, 3/173), polysomy (8.1%, 14/173), and TFF-1 expression (2.7%, 10/273). Interestingly, any case of adenocarcinoma and SCC with TFF-1 amplification harbored positive TFF-1 expression. Conclusion: Both TFF-1 amplification and TFF-1 expression were more common in adenocarcinoma. However, they had distinct prognostic roles: TFF-1 amplification was an independent poor prognostic factor in adenocarcinoma, whereas TFF-1 expression was a favorable prognostic factor.

Keywords: gene copy number, TFF-1, prognostic marker, amplification

Poster Session 1: P1.05: Early Stage NSCLC Translational Research & Biomarkers – Monday, December 5, 2016

P1.05-011 COMPARATIVE ANALYSIS OF TFF-1 COPY NUMBER ALTERATIONS AND PROTEIN EXPRESSION IN PATIENTS WITH NON-SMALL CELL LUNG CANCER

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Background: TFF-1 (also known as NKX2-1) is located at chromosome 14q34.3. TFF-1 is a master regulator for the development of normal lung, and is also both a lineage oncogene and a suppressor gene in non-small cell lung cancer (NSCLC). TFF-1 expression is associated with a favorable prognosis. In contrast, the clinical significance of increased TFF-1 gene dosage has yet to be fully elucidated. We explored the relationship of TFF-1 copy number alterations with TFF-1 protein expression as well as patients' prognoses in a relatively large cohort. Methods: We assessed TFF-1 gene copy number and protein expression in microarrayed 636 NSCLC, including 421 adenocarcinomas and 173 squamous cell carcinomas (SCCs), and 42 other histologies, using fluorescent in situ hybridization and immunohistochemistry. TFF-1 copy number alterations were divided into three categories: amplification (TFF-1/CEP14 > 2), polysomy (TFF-1/CEP14 > 2 and TFF-1 signals > 4 copies per nucleus), and disomy (the others). Their associations with clinical data were retrospectively analyzed. Results: Among the entire cohort, TFF-1 amplification and polysomy were observed in 5.6% (36/636) and 8.3% (53/636), respectively. Tumors with copy number alterations (amplification and polysomy) were detected in 14.5% (91/624) among adenocarcinomas, 9.3% (17/173) among squamous cell carcinomas, and 26.2% (11/42) among other histologies (P = 0.012). TFF-1 expression was almost exclusively observed in adenocarcinomas (P < 0.001). In the adenocarcinoma cohort, the frequency was 6.7% (28/421) for TFF-1 amplification and 7.8% (33/421) for polysomy. TFF-1 positivity was 34.8% (357/1021). A multivariate Cox hazards model analysis demonstrated that TFF-1 amplification was an independent worse prognostic factor (hazard ratio (HR), 3.84; 95% confidence interval (CI), 2.18-6.71) for overall survival, but TFF-1 expression was adversely an independent better prognostic factor (HR, 0.69; 95% CI, 0.29-0.85). In the SCC cohort, there were few cases of TFF-1 amplification (1.7%, 3/173), polysomy (8.1%, 14/173), and TFF-1 expression (2.7%, 10/273). Interestingly, any case of adenocarcinoma and SCC with TFF-1 amplification harbored positive TFF-1 expression. Conclusion: Both TFF-1 amplification and TFF-1 expression were more common in adenocarcinoma. However, they had distinct prognostic roles: TFF-1 amplification was an independent poor prognostic factor in adenocarcinoma, whereas TFF-1 expression was a favorable prognostic factor.

Keywords: gene copy number, TFF-1, prognostic marker, amplification
known as Cancer Stem Cells (CSCs), which are able to grow as spheroids (suspension culture). The aim of the study was to obtain tumorspheres from lung cancer cell lines and to use them as an in vitro platform for drug screening. Methods: Cells from lung cancer cell lines (A549, H1650, PC3, H460 and H358) were grown in monolayer and as spheroids. Cultured cells were used: (i) to compare the cytototoxic effect of anticancer drugs in adherent vs lung-tumorspheres (ii) to perform a high-throughput screening with a commercial chemical library (Prestwick) and (iii) to analyze the cytotoxicity of specific inhibitors of Wnt. Hedgeshop and Notch pathways. Results: Tumorspheres were plated at the desired density in 200 μl of medium in 96-well plates and compounds were added at 4 different concentrations (n=3). Cell viability was measured after 48 and 72h, using MTS Assay. Cell viability was normalized to the respective mock-treated control cells and presented as percentage of control. Results: Cells cultured in suspension conditions were able to form spheroids, such as stem-like cells. Under these culture conditions, classical anticancer drugs (cisplatin, paclitaxel, vinorelbine and pemetrexed) exhibited mild or null cytotoxic effects on A549, H1650, PC3, H460 and H358 spheroids. Moreover, we performed a high-throughput screening with Prestwick library and remarkably, three compounds reduced the number of viable cancer cells. As regards ‘stemness’ inhibitors, Wnt (IWP2 and XAV939) and Hedgehog inhibitors (Vismodegib) show high activity against tumorspheres (p<0.05), suggesting them as possible therapeutic strategies in NSCLC Conclusion: Our data suggest that lung-tumorspheres showed resistance to classical anticancer drugs, strengthening its possible use as a short-term culture platform for a simple, and cost-effective screening to investigate novel therapeutic approaches. In this setting, some compounds were identified as promising therapeutic agents on lung tumours, but confirmatory data are still necessary. This project was supported by (RD12/0036/025) from RTICC, SEOM 2012, (PI12/02383 and PI15/00753) from ISCIII,

Conclusion: Patients harboring an EGFR-mutation in completely resected stage I lung adenocarcinoma had a much improved prognosis compared to those patients whose tumors expressed EGFR wild-type. The presence of an EGFR mutation was a significant positive prognostic factor in this cohort.

Keywords: lung cancer, EGFR, survival, Early-stage
lines showed increased levels of genes related to CSCs properties. Genes belonging to Notch and Wnt signaling pathways were found to be more expressed in tumours, suggesting that these pathways could be interesting for CSC targeting. This work was supported in part, by grants R12/0036/0025 from RTICC, and P12-0238/BH15-0752 from ISCIII.

Keywords: non-small cell lung cancer, biomarker, Gene Expression, Cancer stem cell

POSTER SESSION I - P.01:05. EARLY STAGE NSCLC TRANSLATIONAL RESEARCH & BIOMARKERS – MONDAY, DECEMBER 5, 2016

P1.05-015 GENOMIC CHARACTERISATION OF NON-SMALL CELL LUNG CANCER IN AN AUSTRALIAN POPULATION

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Background: Lung cancer is a heterogeneous disease with poor prognosis. Genomic variants may predict sensitivity to targeted drug therapies or assist in prognosis. We sought to determine the frequency of driver mutations and gene rearrangements in non-small cell lung cancer (NSCLC) and evaluate the feasibility of the MassARRAY system for multiplexed mutational profiling. Methods: A cohort study of 419 fresh-frozen NSCLC tumours was performed (AC, n=370; SCC, n=39; ASC, n=7; LCC, n=3). High-throughput and multiplexed mutational profiling was performed using the MassARRAY genotyping system (Agena Bioscience) (n=419). The OncoFOCUS+KIT panel was used for detecting genomic variants in EGFR, BRAF, KRAS, NRAS and KIT (n=443) and the LungFOCUS panel for fusion genes involving ALK, RET and ROS1 (n=371). Clinico-pathological associations were evaluated using Fisher's exact test for categorical data, and T test for continuous data. A p-value of <0.05 (two-tailed) was considered statistically significant. Results: At least one genomic variant was detected in 196 (46.8%) cases (n=419). EGFR mutations were identified in 42 cases (10.2%), KRAS in 133 (32.3%), BRAF in 11 (2.7%), NRAS in 4 (1.0%) and no KIT mutations were detected. Gene rearrangements involving ALK, RET and ROS1 were identified in 2 (0.5%), 1 (0.3%) and 5 (1.3%) cases respectively. Based on current clinical guidelines for NSCLC, 28 patients would qualify for tyrosine kinase inhibitor therapy, and 4 for targeted therapy available for other cancers (BRAF V600E). EGFR mutations were significantly associated with adenosccinoma histology and female never smokers (p<0.001) and KRAS mutations predominated in smokers (p<0.001). Conclusion: Driver mutations were detected in 46.8% of NSCLC cases resected at TPC1. Rapid, multiplexed mutation testing can guide treatment as well as assist in patient stratification for clinical trials.

Keywords: Epidermal growth factor receptor, Anaplastic lymphoma kinase, non-small cell lung cancer, multiplex genotyping

POSTER SESSION I - P.01:05. EARLY STAGE NSCLC TRANSLATIONAL RESEARCH & BIOMARKERS – MONDAY, DECEMBER 5, 2016

P1.05-016 CIRCULATING BARD1 ANTIBODIES FOR EARLY DETECTION OF LUNG CANCER

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Background: In a study of more than 100 NSCLC cases we previously showed that the expression of BARD1 isoforms is correlated with poor patient survival. BARD1 is a tumor suppressor acting with BRCA1 as ubiquitin ligase. BARD1 has also functions in mitosis and poly(ADP)-ribose signaling for DNA repair. In cancer cells BARD1 isoforms are generated by alternative splicing. SNP affecting splicing and cancer predisposition were identified in neuroblastoma. The alternatively spliced isoforms lack tumor suppressor functions and act as oncogenes. As the domain composition of cancer-associated isoforms predicts altered tertiary structures, we investigated whether BARD1 isoforms act as cancer antigens. Methods: ELSA assays were performed to detect antibodies generated against BARD1 isoforms in the serum of lung cancer patients. We used BARD1 protein fragments and short peptides for capturing autoimmune antibodies. Using fitted Lasso logistic regression methods, we developed an algorithm for the prediction of lung cancer based on a blood test for detection of BARD1 antibodies. Results: Modeling values from 200 samples, shows a distinction of lung cancer and healthy controls with high sensitivity and specificity (AUC=0.961; Figure 1). Splitting the samples randomly and repeatedly into training sets and validation sets, confirmed an average AUC=0.964 for the training sets and AUC=0.861 for the validation sets. ROC curves for early and late stage lung cancers showed no difference in their AUCs. The BARD1 lung cancer test is highly specific and does not cross-react with other cancers. Conclusion: Lung cancer is a very long latent disease at an asymptomatic and untreatable stage. Currently the detection by low dose CT scan is relatively expensive and not very specific. Therefore a blood test, such as the BARD1 test could i) help to detect cancers earlier, in particular by screening of risk groups, and ii) become a diagnostic aid in combination with CT scan.

Keywords: Early detection, lung cancer, biomarker

Figure 1. ROC curve showing BARD1 lung cancer test sensitivity and specificity.

POSTER SESSION I - P.01:05. EARLY STAGE NSCLC TRANSLATIONAL RESEARCH & BIOMARKERS – MONDAY, DECEMBER 5, 2016

P1.05-017 THE PROGNOSTIC IMPACT OF EGFR, KRAS AND TP53 MUTATIONS IN CURATIVELY RESECTED EARLY-STAGE LUNG ADENOCARCINOMAS

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Background: As the 5-year survival among individuals undergoing curative-intent resection for early-stage lung cancer approaches 50%, identification of prognostic biomarkers useful for risk stratification is a priority. While somatic mutation profiling drives treatment choice in advanced disease, its usefulness among early-stage patients is not well-established. Methods: From May 2011 through December 2014, the Yale Lung Cancer Group operated on 592 individuals who underwent curative-intent complete resection for Stage I-IIIA adenocarcinoma. Demographics and lifestyle choices were ascertained by interview using validated questionnaires. Pathologic characterization of index tumors, including CLIA Laboratory-assayed EGFR/KRAS status, was extracted from the medical record. A custom targeted resequencing panel covering all coding exons from 93 lung adenocarcinoma-related genes was designed. Buffy coat-derived germline DNA and tumor DNA, extracted from the FFPE surgical specimen, were sequenced on the Ion Torrent platform with >90% of the assayed amplicons achieving >30x coverage in both tumor and germline from each case. Somatic non-synonymous tumor variants were identified using the Torrent Variant Caller. Bivarate associations were calculated using Fisher's exact test for categorical data, and T test for continuous data. A p-value of <0.001 (two-tailed) was considered statistically significant. Results: At least one genomic variant was detected in 196 (46.8%) cases (n=419). EGFR mutations were identified in 42 cases (10.2%), KRAS in 133 (32.3%), BRAF in 11 (2.7%), NRAS in 4 (1.0%) and no KIT mutations were detected. Gene rearrangements involving ALK, RET and ROS1 were identified in 2 (0.5%), 1 (0.3%) and 5 (1.3%) cases respectively. Based on current clinical guidelines for NSCLC, 28 patients would qualify for tyrosine kinase inhibitor therapy, and 4 for targeted therapy available for other cancers (BRAF V600E). EGFR mutations were significantly associated with adenocarcoma histology and female never smokers (p<0.001) and KRAS mutations predominated in smokers (p<0.001). Conclusion: Driver mutations were detected in 46.8% of NSCLC cases resected at TPC1. Rapid, multiplexed mutation testing can guide treatment as well as assist in patient stratification for clinical trials.

Keywords: Early detection, lung cancer, biomarker

Figure 1. ROC curve showing BARD1 lung cancer test sensitivity and specificity.
Abstracts

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(p=0.0007). Seventy-two percent of EGFR and 81.7% of KRAS mutations were found among female patients (p=0.0008). The joint distribution between smoking and gender favored EGFR mutations among female never/former smokers. KRAS mutations among female ever-smokers and EGFR/KRAS wild-type status among male ever-smokers (p=0.0002). After adjustment for ACC2−/− edition Tstage, Nstage and presence of lymphovascular invasion, KRAS mutations (HR=2.16, 95% CI 1.04–4.43; p=0.04) but not EGFR mutations (p=0.63) were prognostic for poorer disease-free survival. Targeted resequencing data is available on 148 cases. The nonsynonymous mutation burden ranged from 0.7 with 84% of cases having ≥3. In addition to KRAS and EGFR, frequent mutations were noted in p53 (n=60, 27.0%), STK11 (n=10, 6.8%) and PIK3CA (n=7, 4.7%) with 4 genes mutated in 6 cases. TP53 mutations (p=0.63) were prognostic for poorer disease-free survival. Targeted resequencing data is available on 148 cases.

Keywords: recurrence-free survival, TP53, KRAS, Somatic mutation

P1.05-018 LINC0016 IS A POTENTIAL BIOMARKER FOR EARLY-STAGE LUNG CANCER THAT PROMOTES CELL PROLIFERATION BY REGULATING THE CELL CYCLE
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Background: Early diagnosis of lung cancer greatly reduces mortality; however, the lack of suitable plasma biomarkers presents a major obstacle. Recent studies showed that long noncoding RNAs (lncRNAs) play important roles in cancer initiation and development. Methods: Here, we identified differentially expressed lncRNAs by using custom designed microarray on 20 lung cancer samples and evaluated the expression by Real-time PCR (qRT-PCR) on 118 lung cancer samples. The role of lncRNA16 in lung cancer was studied in vitro and in vivo, utilizing the lung cancer cell line PC9, A549 and xenograft mouse models. Results: lncRNA16 (ENST00000539303) expression level was highly correlated with early stage lung cancer (Spearman’s rho = 0.77) and in plasma (Spearman’s rho = 0.62) of lung cancer patients. In early stage, lncRNA16 expression levels were significantly higher compared to that in adjacent matched normal tissues (Figure 1C-1F). Importantly, this increase was mirrored in plasma samples of early stage lung cancer patients (Figure 2A). Our study reveals that knockdown of lncRNA16 inhibited proliferation of PC9 cells in vitro and also inhibited tumor growth in xenograft mouse models. Specifically, we showed that lncRNA16 promotes G2/M transition through regulating cyclin B1 transcription. Conclusion: In conclusion, lncRNA16 was identified as a potential biomarker for lung cancer diagnosis, as it displayed significantly elevated levels in cancer patient over baseline. Furthermore, we showed that the false-negative rate is significantly lower compared to markers those widely used for lung cancer assessment.

Keywords: lncRNA, Lung cancer, Biomarker

POSTER SESSION 1: P1.05: EARLY STAGE NSCLC TRANSLATIONAL RESEARCH & BIOMARKERS – MONDAY, DECEMBER 5, 2016

P1.05-019 TWO INFLAMMATORY BIOMARKERS MDC/CCL2 AND BLC/CXCL13 ARE INDEPENDENTLY ASSOCIATED WITH THE SIGNIFICANT RISK OF EARLY STAGE LUNG ADENOCARCINOMA
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Background: This prospective study was designed to investigate the association between multiple inflammatory biomarkers in circulation and the risk for early stage lung adenocarcinoma. Methods: We measured 10 inflammatory biomarkers in 228 early stage lung adenocarcinoma patients and 228 age and smoking matched healthy controls by using the luminex bead-based assay. Results: Only two biomarkers were significantly associated with early stage lung adenocarcinoma risk after Bonferroni correction: the multivariate odd ratio or OR (95% confidence interval or CI) was 0.29 (0.16–0.53) for MDC/CCL2 (P<0.0001) and 4.17 (2.23–7.79) for BLC/CXCL13 (P<0.0001) for the comparison of 4th quartile with 1st quartile. When analysis was restricted to never smokers (196 patients/196 controls), MDC/CCL2 and BLC/CXCL13 were still significantly associated with early stage lung adenocarcinoma risk (OR; 95% CI; P<0.03; 0.21–0.66; P<0.0001 for MDC/CCL2 and 2.78; 1.48–5.22; P<0.001 for BLC/CXCL13). Additionally, significance persisted after restricting analysis to 159 stage IA lung adenocarcinoma patients and 159 matched controls for MDC/CCL2 (OR; 95% CI; P<0.03; 0.21–0.66; <0.0001) and BLC/CXCL13 (2.78; 1.48–5.22). Furthermore, elevated BLC/CXCL13 was associated with the risk of subcentimeter lung adenocarcinoma, and there was an increasing trend for BLC/CXCL13 with the progression of subcentimeter lung adenocarcinoma. Conclusion: Our findings demonstrated that MDC/CCL2 and BLC/CXCL13 were independently associated with the significant risk of early stage lung adenocarcinoma, and this risk was higher in female patients than male patients. Moreover, BLC/CXCL13 was identified to play a carcinogenic role in the progression of lung adenocarcinoma.

Keywords: Early Stage Lung Adenocarcinoma, Subcentimeter lung adenocarcinoma, Inflammatory biomarkers, Prospective study

POSTER SESSION 1: P1.05: EARLY STAGE NSCLC TRANSLATIONAL RESEARCH & BIOMARKERS – MONDAY, DECEMBER 5, 2016

P1.05-020 OPPOSING PROGNOSTIC ROLES OF CD73 AND A2A ADENOSINE RECEPTOR IN NON-SMALL-CELL LUNG CANCER
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Background: CD73 (otherwise known as ecot-s5'-nucleotidase) is an important molecule in the adenosine pathway because it generates adenosine by enzymatically dephosphorylating extracellular AMP, which results in immunosuppressed niche within the tumor microenvironment. A2A adenosine receptor (A2AR) acts as a predominant receptor for adenosine in immune cells and can also be expressed in lung tumor cells. However, the clinical impact of the adenosine pathway in non-small-cell lung cancer (NSCLC) has yet to be uncovered, although the pathway has been shown to have a pivotal role in the regulation of anti-tumor immunity and is considered as one of the promising future treatment targets. Methods: We measured CD73 and A2AR protein expression profiles using immunohistochemistry in tissue microarrays containing 642 resected NSCLC specimens. The expression levels were assessed using the H-score method that ranged from 0 to 300, and cutoffs were determined using the minimum P-value method for overall survival (OS). The associations between their expression levels and clinicopathological and molecular characteristics as well as patients’ prognoses were retrospectively analyzed. Results: The median age of patients was 68 years old (range, 23–88) and 440 (68.5%) patients were men. 438 (68.2%) patients had smoking history and 420 (65.4%) patients had adenocarcinoma histology. Significantly higher expression of both CD73 and A2AR was observed in female than male, in never smokers than ever smokers, and in adenocarcinomas than squamous cell carcinomas. Among adenocarcinomas, both high CD73 and A2AR expression were significantly associated with TTF-1 positivity and EGFR mutations. ALK-positive adenocarcinomas showed significantly higher expression levels of CD73 than ALK-negative tumors. High CD73 expression was an independent indicator of a poor prognosis for NSCLC patients in multivariate Cox regression analyses for OS (hazard ratio (HR), 2.19; 95% confidence interval (CI), 1.38–3.47) and disease-specific survival (DFS) (HR, 2.07; 95% CI, 1.78–2.41). Contrary, high A2AR expression was an independent favorable predictor of prognosis for OS (HR, 0.69; 95% CI, 0.69–0.97) and DFS (HR, 0.51; 95% CI, 0.33–0.79). Among adenocarcinomas, high CD73 expression was an independent poor prognostic marker for OS (HR, 2.79; 95% CI, 1.61–4.63) and DFS (HR, 4.37; 95% CI, 2.54–8.23), whereas high A2AR expression was an independent favorable prognostic marker for DFS (HR, 0.56; 95% CI, 0.32–0.98). Conclusion: Both CD73 and A2AR expression was associated with TTF-1-positive and EGFR-mutant adenocarcinoma. Nonetheless, they had opposing prognostic significance in resected NSCLC.

Keywords: adenosine, CD73, Prognosis, A2AR
Dublin/Ireland, might be reduced dramatically when the disease and its metastatic spread are assessed for circRNAs. At present we are validating the expression of n=206 circRNAs with a 2-fold difference in expression between their matched normal vs. tumour counterparts. Principal Component Analysis (PCA) demonstrated a clear separation of the samples (tumour vs. Normal). Self-Organizing Maps (SOMs) analysis generated distinctive SOMS clusters of circRNAs, while associated linear pathway enrichment for microRNA and transcriptional binding motifs identified several additional potential networks. Moreover, an analysis of linear mRNAs associated with 10 circRNAs matched normal vs. tumour counterparts. Principal Component Analysis

Background: The relevance of programmed cell death ligand 1 (PD-L1) to patient-derived xenograft (PDX) formation and clinicopathological characteristics in early stage lung cancer was studied Methods: Cell counting kit-8 and flow cytometry were carried out to examine proliferation and apoptosis in PC9 and H520 cells transfected with siRNAs. Nod-scid mice were used to establish PDX. Immunohistochemistry was done to investigate PD-L1 expression in tumor tissues. Results: Proliferation was reduced and apoptosis was induced when PD-L1 was inhibited in the cells. Higher PD-L1 expression was observed in the primary tumors with PDX formation than in the tumors without PDX formation. Moreover, PD-L1 was found to be related to smoking, histological types, stages and overall survival in 209 of lung cancer patients. Conclusion: This study suggests that PD-L1 promotes PDX formation ability and is an independent prognostic marker for the early stage lung cancer patients.

Keywords: PD-L1, Patient-derived xenograft, lung cancer, clinical significance

P1.05-023 INDUCTION OF PATIENT-DERIVED XENOGRAFT FORMATION AND CLINICAL SIGNIFICANCE FOR PD-L1 IN LUNG CANCER PATIENTS
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Background: The relevance of programmed cell death ligand 1 (PD-L1) to patient-derived xenograft (PDX) formation and clinicopathological characteristics in early stage lung cancer was studied Methods: Cell counting kit-8 and flow cytometry were carried out to examine proliferation and apoptosis in PC9 and H520 cells transfected with siRNAs. Nod-scid mice were used to establish PDX. Immunohistochemistry was done to investigate PD-L1 expression in tumor tissues. Results: Proliferation was reduced and apoptosis was induced when PD-L1 was inhibited in the cells. Higher PD-L1 expression was observed in the primary tumors with PDX formation than in the tumors without PDX formation. Moreover, PD-L1 was found to be related to smoking, histological types, stages and overall survival in 209 of lung cancer patients. Conclusion: This study suggests that PD-L1 promotes PDX formation ability and is an independent prognostic marker for the early stage lung cancer patients.

Keywords: PD-L1, Patient-derived xenograft, lung cancer, clinical significance

P1.05-024 PREOPERATIVE NEURON-SPECIFIC ENOLASE TO ALBUMIN RATIO IS A PROGNOSTIC BIOMARKER FOR PATIENTS WITH OPERABLE NON-SMALL-CELL LUNG CANCER
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Background: Neuron-specific Enolase (NSE) is a widely used tumor biomarker in small-cell lung cancer (SCLC) diagnosis, and serum albumin (Alb) levels are commonly used as indicators of the nutritional status of cancer patients. However, the prognostic value of these markers in combination has not been examined. This study was designed to explore the value of the combination between NSE and Alb in non-small-cell lung cancer (NSCLC). Methods: We retrospectively evaluated the prognostic value of the preoperative NSE to albumin ratio (NAR) in 319 patients with operable NSCLC. We analyzed associations among the NAR, clinicopathological characteristics, and inflammatory biomarkers. Univariate and multivariate analyses were performed to identify the clinicopathological characteristics associated with OS. Furthermore, we compared the prognostic value of the NAR with other established prognostic indexes by evaluating the area under the curves (AUC). Results: The optimal NAR cutoff level was found to be 3.2 ± 0.7. We found that a higher NAR was associated with more advanced TNM staged cancers (P=0.041) and higher tumor stage (P=0.011). The NAR was also associated with the inflammatory biomarker albumin/globulin ratio (AGR, P=0.032), but not the neutrophil/lymphocyte ratio (NLR, P=0.295) or platelet/lymphocyte ratio (PLR, P=0.260). In multivariate analyses, the NAR was an independent prognostic factor for NSCLC patients (P=0.001). The AUC of the NAR was higher than the NLR, PLR or AGR at 24 and 36 months of follow-up. Conclusion: The preoperative NAR might be an independent prognostic
factor for patients with operable NSCLC, and a higher NAR indicates a poorer prognosis.

Keywords: Non-small-cell lung cancer, Neuron-specific Enolase, albumin, Prognosis

P1.05-025 PROGNOSTIC SIGNIFICANCE OF HEPATITIS B VIRUS TO STAGE IB NON-SMALL CELL LUNG CANCER PATIENTS IN CHINA
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Background: Hepatitis B virus (HBV) is considered to be a major cause of hepatocellular carcinoma. However, little is known about the role of chronic HBV infection in other malignancies. We aimed to investigate HBV infection with other well-established prognostic factors and performed multivariate survival analyses to evaluate its value in Chinese non-small cell lung cancer (NSCLC) patients. Methods: It is a retrospective evaluation of the impact of HBV infection status in 366 patients who underwent complete surgical resection for stage IB NSCLC NSCLC patients in Shanghai Chest Hospital from 1998 to 2008. All the patients were Shanghai Niece and all the stage IB NSCLC patients didn't receive adjuvant chemotherapy. The patients' blood samples were tested with chemiluminescent immunoassay for the presence of HBV surface antigen (HBsAg), antibodies against HBV core antigen (anti-HBc), and antibodies against HBV DNA (anti-HBc) before operation. Other variables in the analysis included age, gender, history of smoking and pathologic type. HBsAg positive was defined as HBV infection. Results:

S1 HBV infection cases (13.93%) were positive in stage IB NSCLC. The 5-year overall survival of patients with or without chronic HBV infection were 71.25% and 50.98% (P=0.028). Multivariate analyses revealed that gender, chronic HBV infection were significant predictive factors for overall survival (P<0.05). Conclusion: The chronic HBV infection is a significant independent prognostic factor in stage IB non-small cell lung cancer.

Keywords: Hepatitis B Virus, non-small cell lung cancer

P1.05-026 HIGH RESOLUTION METABOLOMICS ON EXHALED BREATH CONDENSATE TO DISCOVER LUNG CANCER’S BIOMARKER
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Background: Early and non-invasive detection of lung cancer is a desirable prognostic tool for prevention of lung cancer at early stages. Previously, unusual human breath smell of lung cancer patients detected by trained dogs played an important role in early detection of lung cancer. Which suggests that exhaled breath condensate (EBC) is a promising source for searching potential biomarkers in lung cancer patient. Methods: EBC sample collected using specific device called R-tube, containing both the volatile organic compounds (VOCs) and non-volatile organic compounds (NVOCs), were obtained from patients with lung cancer (n = 20) and non-malignant healthy individuals (n = 5). The EBC samples were applied to high resolution metabolomics (HRM) based LC-MS for comparison of metabolic differences among healthy people and lung cancer patients in order to detect potential biomarkers. The multivariate statistical analysis was performed, including a false discovery rate (FDR) of q<0.05, to determine the significant metabolites between the groups. 2-way hierarchical clustering analysis (HCA) was done for determining the classification of significant features between the control healthy and lung cancer patients. The significant features were annotated using Metlin database (metlin.scripps.edu/) and the identified features were then mapped on the human metabolome pathway database (Human Metabolome Database, HMDB) and additional validation cohorts from two prospective cooperative group studies. Results: The metabolomics-wide associated study (MWAS), metabolic changes among healthy group and lung cancer patients were detected. The 2-way HCA identified different metabolic profile in lung cancer patients from healthy control. The identified potential biomarkers are Acetophenone (m/z 103.0542, [M+H-H2 O]+), P-tolualdyde (m/z 138.0914, [M+Na]+), 2,4,6-Trichlorophenol (m/z 218.9134, [M+Na]+) and 11(R)-HETE (m/z 343.2233, [M+Na]+). The top 5 of affected KEGG pathways are Arachidonic acid metabolism, Glycerophospholipid metabolism, Bile secretion, Inflammatory mediator regulation of TRP channels and Tyrosin metabolism. Conclusion: Our result shows that Acetophenone, P-tolualdyde, 2,4,6-Trichlorophenol and 11(R)-HETE are significantly higher in lung cancer patients. Acetophenone and 2,4,6-Trichlorophenol are classified as a Group D human carcinogen approved by US Environmental Protection Agency (EPA), while 11(R)-HETE is associated with Arachidonic acid metabolism and P-tolualdyde is related to xylene degradation pathway and degradation of aromatic compounds pathway. Our identified metabolites can be the potential biomarkers in EBC for the early and non-invasive detection of lung cancer.

Keywords: exhaled breath condensate, metabolomics, Liquid chromatography (LC-MS/MS), lung cancer
prognostic models were generated (see Figure): Pooled Model A (PMA) was the optimal 2-cluster model using probesets representing 6 genes selected from components of pre-existing signatures: CASP8, MDM2, SEL1L3, RCLP1, LRR1, COPZ2. Pooled Model B (PMB) was the optimal 2-cluster model using probesets representing 6 genes selected from among all those profiled: SSX1, DIAF3, LOC619427, CASP8, EEF251, HSPA13. PMA and PMB each remained independently prognostic in multivariable analyses incorporating an a priori baseline model (age, sex, stage; c-index = 0.641). Conclusion: Two de novo prognostic signatures were derived using a pooled multi-institutional cohort of SCC assembled for validation of pre-existing signatures. PMA and PMB were each found to be independently prognostic, accounting for established clinical predictors. Both now move forward, along with validated pre-existing cohorts of cases.

Keywords: gene expression signature, Squamous cell lung cancer

POSTER SESSION 1 - P1.05: EARLY STAGE NSCLC

P1.05-029 SABRTOOTH-A FEASIBILITY STUDY OF SABR COMPARED TO SURGERY IN PATIENTS WITH PERIPHERAL STAGE I NSCLC CONSIDERED TO BE AT HIGHER RISK FROM SURGERY

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Background: Stereotactic Ablative Radiotherapy (SABR) is a well established treatment for medically inoperable peripheral stage I NSCLC. Previous non-randomised evidence supports SABR as an alternative to surgery, but high quality randomised control trial (RCT) evidence is lacking due to low

Keywords: NSCLC, TIL, Tumor infiltrating lymphocytes

POSTER SESSION 1 - P1.05: EARLY STAGE NSCLC

SBRT – MONDAY, DECEMBER 5, 2016
recruitment. The UK SABRtooth study aims to see if a large RCT is feasible. Methods: The trial management group includes pulmonologists, thoracic surgeons, nurses, patient representatives, oncologists and statisticians. Patients consist of patients at highest risk of operative mortality and morbidity with a peripheral stage I (≤3cm) NSCLC are eligible. Defining “higher-risk” patients considers multiple criteria, but the final decision is left to the individual tumour boards. Equipoise in presenting the two interventions to patients was considered key. Bias is minimised by ensuring the initial approach is by the pulmonologist with subsequent counseling by the research nurse and randomisation occurring before consultation with a surgeon or oncologist. Patients who decline the trial or do not proceed with their allocated treatment are invited to take part in qualitative interviews. The trial is open in 4 thoracic oncology centres and their referral units. The aim is to recruit on average 3 patients/month to demonstrate that a phase III RCT would be feasible. Results: Following a launch meeting in April 2015 the trial opened in July (all centres opened October 2015). To help train research staff with introducing the trial to patients, mock patient consultations were recorded. Recruitment was initially slow. Specific research nurse meetings have taken place (December 2015 and June 2016) to understand the barriers to recruitment, centre-specific issues and provide additional education to improve nurses’ confidence in recruiting patients. Regular updates are provided with monthly emails and In February 2016, the Chief Investigator and Trial Manager visited each site to promote the trial and help with any local barriers to recruitment. In response to feedback, changes to the protocol to aid patient recruitment, additional promotional and patient information provided and a video for patients were produced. The study has also been presented at various Oncology/thoracic meetings. As a result recruitment has increased significantly and is successfully continuing in the trial. Conclusion: Whether SABR is an alternative to surgery is a key question in stage I NSCLC. However, SABRtooth is a challenging study but with a novel trial design and continual adaptive feedback we hope to be able to meet recruitment targets and demonstrate that a definitive phase III RCT is feasible.

Keywords: SABR, Surgery, Stage I NSCLC, Randomised Controlled trial
evaluated by using the 30-item European Organization for Research and Treatment of Cancer Quality of life Core questionnaire and its corresponding 13-item lung cancer supplement. A linear mixed model was used to analyze the data and a change of more than five points was determined as minimal clinically important difference. Results: Ninety-three patients were included (SBRT n = 39, surgery n = 54). Patients who underwent SBRT were significantly older, had a higher ECOG performance status and a lower pulmonary function. The compliance for SBRT and surgery at baseline were 97% and 98% (p = 0.8), at three months 74% and 71% (p = 0.8), at six months 62% vs 78% (p = 0.3), and at 12 months 45% and 73% (p = 0.04). The ECOG performance status was not significantly different between the patients who were compliant and those who were not compliant. During the 12 months after treatment different significant changes were observed:

- QoL remained stable in SBRT patients and increased in surgical patients (p = 0.012)
- Role functioning increased in SBRT patients and decreased in surgical patients (p = 0.005)
- Cognitive functioning increased in SBRT patients and remained stable in surgical patients (p = 0.045)
- Social functioning remained stable in SBRT patients and decreased in surgical patients (p = 0.001)
- Pain increased in SBRT patients and decreased in surgical patients (p = 0.001)

SBRT patients had a decrease in effect of pain medication and surgical patients had an increase in effect of pain medication (p = 0.0001).

Conclusion: We showed that in patients with early stage NSCLC treated with SBRT or surgery the QoL scores showed different changes after treatment. In the light of the comparable clinical outcomes after both treatments these QoL aspects should be discussed with the patient before making a treatment decision.

Keywords: early stage non-small cell lung cancer, stereotactic body radiotherapy, surgery, quality of life

P1.05-033 COMPARISON OF SINGLE- AND FIVE-FRACTION SCHEDULES OF STEREOTACTIC BODY RADIATION THERAPY FOR CENTRAL LUNG TUMORS

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Background: Stereotactic Body Radiation Therapy (SBRT) is a treatment option for patients with early-stage non-small cell lung cancer (NSCLC) who are medically inoperable or decline surgery. The safety of 20 Gray (Gy) x 4 fractions of SBRT to within 2 cm of the proximal bronchial tree is unclear. Here we compare the clinical outcome of patients with centrally located lung tumors who underwent either single fraction (SF)- or five-fraction (FF-) SBRT at a single institution over 5 years. Methods: Between January 2009 and October 2014, 11 out of 42 patients received 26-30 Gy in 1 fraction, while the remaining 31 patients received 52.5-60 Gy (median 55 Gy) in 5 fractions. Data were retrospectively collected using an institutional review board-approved database. Kaplan-Meier method, competing risks method, and Cox regression model were used. Toxicities were graded using Common Terminology Criteria for Adverse Events version 4.0. R version 3.3.1 was used for statistical analysis. Results: After a median follow-up of 12 months of SF-SBRT and 17 months for FF-SBRT groups (p=0.64), 1-year overall survival rates for SF- and FF-SBRT groups were 82% and 87%, respectively. There was no statistically significant difference in overall survival (p=0.061), progression-free survival (p=0.47), local failure (p=0.43), nodal failure (p=0.62), and distant failure (p=0.45) at 18 months. No primary tumor failure was seen in both groups at 18 months. Distant failure rates at 18 months were 9.1% for SF-SBRT group and 54.5% for FF-SBRT group. Among the patients with distant failure (n=4 in SF-SBRT and n=6 in FF-SBRT), median time to distant failure was 29.5 months and 8.9 months for SF- and FF-SBRT groups, respectively (p=0.0095). 3 out of 11 patients in SF-SBRT group and 2 out of 32 patients in FF-SBRT group experienced grade 3-4 toxicities. No grade 4-5 toxicities were observed in the SF-SBRT group. SF-SBRT group showed higher cumulative incidence of grade 3+ toxicities at 18 months (p=0.018). However, univariate analysis showed SF-SBRT alone was not a significant factor that increased risk for grade 3+ toxicities (HR=5.50, p=0.063). 4 out of 5 toxicities occurred at least 12 months after SBRT. Conclusion: SF- and FF-SBRT showed no significant difference in overall survival and local control. No grade 4-5 toxicities were observed in our FF-SBRT group. The onset of distant failure was significantly delayed in the SF-SBRT compared to the FF-SBRT group. The majority of toxicities occurred late. Having SF-SBRT itself was not significantly associated with severe toxicity.

Keywords: Distant failure, Stereotactic body radiation therapy, Single fraction, Central lung tumor

P1.05-034 NEUTROPHIL-TO-LYMPHOCYTE AND PLATELET-TO-LYMPHOCYTE RATIOS AS PROGNOSTIC BIOMARKERS IN EARLY NSCLC PATIENTS TREATED WITH SABR

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Background: Inflammation may play an important role in cancer progression. High Neutrophil-to-Lymphocyte ratio (NLR) and Platelet-to-Lymphocyte ratio (PLR) have been reported to be poor prognostic indicators in several malignancies. In this study we quantify the prognostic impact of these biomarkers for overall survival (OS) among early stage NSCLC patients treated with Stereotactic Ablative Body Radiotherapy (SABR). Methods: 102 consecutive patients who received SABR between October 2011 and May 2014 at the Beatson West of Scotland Cancer Centre (BWoSCC) were identified from a prospectively maintained electronic database. NLR and PLR were derived from blood results obtained within 60 days prior to SABR. Receiver Operator Characteristic (ROC) curves were generated to calculate the optimal thresholds for NLR and PLR. Results: The median age of patients was 72 (range 47-91) years. 60 (59%) were female. Maximum tumour diameter ranged from 10-42mm (median 18mm). Median follow up was 37.1 months. Overall survival at 2 and 4 years was 75.5% (95%CI 65.9-82.7%) and 51.4% (38.8-62.6%) respectively. There was a strong association between NLR and PLR levels (r=0.803, p=0.001). ROC curves indicated a threshold value for NLR of 3.155 (AUC 0.74) and PLR of 155.15 (AUC 0.70) respectively. Median OS for ‘low’ NLR and PLR was not yet reached compared with 33.9 months for ‘high’ NLR (p<0.0001) and 35.4 months for ‘high’ PLR (p=0.002). Multivariable analysis indicated a stronger independent effect of NLR (p<0.0001), whilst taking account of gender, age, tumour size, histological confirmation and performance status. No association was found between elevated NLR or PLR and loco-regional or distant recurrence. Conclusion: Neutrophil-to-Lymphocyte Ratio appears to be a prognostic biomarker for patients with early stage NSCLC receiving SABR. Platelet-to-Lymphocyte ratio acts as a clinical co-variant. We found no association between elevated NLR or PLR and loco-regional or distant recurrence.

Keywords: SABR, NSCLC

P1.05-035 SABR FOR MEDICALLY INOPERABLE EARLY STAGE NSCLC AT THE BEATSON WEST OF SCOTLAND CANCER CENTRE: OUTCOMES AND TOXICITY

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Background: SABR is now an established therapeutic option for patients with medically inoperable early stage NSCLC. It is well tolerated and associated with low rates of Grade 3+ toxicity. Here we present the outcomes and toxicity data for the SABR service based at the Beatson West of Scotland Cancer Centre (BWoSCC). Methods: All 102 consecutive patients (median age 72 (range 47-91) years, 60 (59%) female) who received SABR between October 2011 and May 2014 at the BWoSCC were identified from a prospectively maintained electronic database. Toxicity data was collected at pre-determined intervals in a dedicated follow-up clinic. Radiological evidence of pneumonitis was scored on follow-up CT imaging at 3 months post-SABR. Outcomes were collated from electronic records. Results: Median and minimum follow-up were 37.1 and 24.3 months respectively. Histological confirmation of NSCLC was available for 33 (32.4%) patients.
Local and regional control rates at 2 years were 95.1% and 94.1% respectively. 8.8% of patients developed metastases within 2 years with a median time to detection of metastases of 6.9 months. Overall survival (OS) at 1, 2, and 4 years was 82.2% (95%CI 80.2-93.1%), 75.5% (65.9-82.7%), 59.8% (48.2-69.7%) and 51.4% (38.8-62.7%) respectively. No difference in OS was apparent between histologically confirmed and unconfirmed subgroups (p=1.0). On multi-variable analysis, tumour size >20mm was negatively associated with OS (p=0.003) whilst gender, age, performance status, deprivation index and histological confirmation were not associated. Radiological scoring of post-SABR pneumonitis was available for 69 patients. A total of 33 of these patients (48%) had radiological evidence of pneumonitis. No association between V5 or V20 and radiological pneumonitis was identified. One death occurred that was potentially related to radiation pneumonitis. Otherwise, only 1 patient experienced grade 4 toxicity (fatigue) and 5 patients (4.9%) reported grade 3 toxicity (4x dyspnoea, 1x fatigue) within 12 months of SABR. There were 4 instances of rib fracture with no association with maximum chest wall dose. Conclusion: While the Westin of Scotland Cancer Centre the use of SABR for early stage NSCLC is associated with high rates of loco-regional control. Our overall survival and toxicity data compare favourably with published series.

Keywords: SABR, NSCLC

POSTER SESSION 1 - P1.05: EARLY STAGE NSCLC SURGERY – MONDAY, DECEMBER 5, 2016

P1.05-036 A PROPENSITY-MATCHED STUDY OF MULTI-PORT VERSUS SINGLE-PORT VIDEO-ASSISTED THORACOSCOPIC SURGERY FOR EARLY LUNG CANCER
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Background: Several thoracic surgeons have already reported the beneficial effects of single-port (SP) video-assisted thoracoscopic surgery (VATS) for the patients with lung cancer. We also analyzed surgical outcomes between SP VATS and multi-port (MP) VATS, which was defined as surgery through 3-4 ports alone, and showed the inhibitory effect of postoperative wound pain in the SP VATS (Eur J Cardiothorac Surg 2015). In this study, we aimed to compare the effectiveness of SP and MP video-assisted thoracoscopic surgery for stage I lung cancer. Methods: A total of 212 patients with non-small cell lung cancer underwent lobectomy via SP and MP procedure between April 2008 and June 2015 in our institute. We examined the a propensity-matched analysis, perioperative variables and short-term outcomes of both operations. Results: Propensity matching produced 80 pairs in each group. The mean Fev0.1 and maximum size of tumor was 1.88±0.32/1.65±0.41 liter and 2.8±0.3/2.7±0.3 cm, respectively. The median operation time, intraoperative blood loss was 165±35/172±26 min. and 85±25/75±26 ml. The median drainage duration and postoperative hospital stay were 19±12/27±14 days and 7.5±1.8/8.1±1.9 days respectively. The median number of dissected lymph nodes was 19±13 vs 17±6 vs 17±6 vs 17±6. The number of days that was used with analgesic agents within a month after surgery was 8±1/1.2±1.2±2±1±5 (P<0.05). Conversion rate to open lobectomy was 3.9% in SP VATS. Conclusion: SP VATS lobectomy, showing almost as effective as the MP VATS should be considered as a new treatment option for stage I lung cancer.

POSTER SESSION 1 - P1.05: EARLY STAGE NSCLC SURGERY – MONDAY, DECEMBER 5, 2016

P1.05-037 HISTOPATHOLOGIC RESULTS OF SURGICALLY RESECTED PURE GROUND-GLASS OPACITY LUNG NODULES
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Background: Little is known about the histopathology of persistent pure ground-glass opacity lung nodules (GGNs). Methods: We reviewed preoperative chest computed tomography (CT) in patients who underwent surgery for GGNs between March 2015 and May 2016. A total of 58 surgically resected pure GGNs persistent more than 3 months and their diameter at CT scan less than 15 mm in 41 patients were included. Then pathologic reports of 58 GGNs were retrospectively reviewed. Results: Median age of the patients was 58 years (range, 33 – 75) and 34 patients (83.3%) were female. Median preoperative follow-up duration of GGNs was 11 months (range, 3 – 114). In spite of all patients were asymptomatic, the reasons of check-up the chest CT included to follow-up for other malignant disease in 29 patients (70.1%), routine health check-up in 10 (25.0%), and to follow-up of other benign disease in 2 (4.9%). Among a total 65 operations, preoperative CT-guided localization was performed in 31 operations (68.9%). Extents of resection included wedge resection in 29 patients (64.4%), segmentectomy in 7 (15.6%), and lobectomy in 9 (20.0%). Lymph node sampling or dissection was performed in 27 operations (60.0%). Among 58 resected GGNs, median diameter of GGNs was 8mm (range, 3 – 15mm), median number of resected GGN per operation was 2 (range, 1-5). The distribution of pathologic diagnosis included benign disease in 3 GGNs (5.2%), atypical adenomatous hyperplasia (AAH) in 4 (6.9%), adenocarcinoma in situ (AIS) in 17 (29.3%), minimally invasive adenocarcinoma (MIA) in 19 (32.8%), and invasive adenocarcinoma (IA) in 15 (25.9%). The diameter of GGNs classified into 3 categories (0 – 5mm, 6 – 10mm, 11 – 15mm) were associated with pathologic invasiveness (Cochran-Armitage test, p = 0.005). However, follow-up duration of GGNs classified into 3 categories (3 – 12 months, 13 – 24 months, more than 25 months) was not associated with diameter of GGNs (p = 0.453) or pathologic invasiveness (p = 0.893). Among 18 GGNs tested, epithelial growth factor receptor (EGFR) mutations were detected in 5 GGNs (27.7%). Conclusion: The prevalence of lung adenocarcinoma (AIS, MIA, IA) was 87.9% in surgically resected pure GGNs persistent more than 3 months and their diameter at CT scan less than 15 mm. A diameter of GGNs diameter was associated with pathologic invasiveness. Further studies are needed for persistent pure GGNs not affected by partial-volume effect of CT in non-selected patients.

Keywords: lung, Adenocarcinoma, GGO, Surgery

POSTER SESSION 1 - P1.05: EARLY STAGE NSCLC SURGERY – MONDAY, DECEMBER 5, 2016

P1.05-038 PATTERNS OF RECURRENCE IN CURATIVELY RESECTED STAGE I LUNG CANCER
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Background: The patterns of recurrence after curative resection for pathologically stage I non-small cell lung cancer(NSCLC) were investigated according to the cell type. Methods: The medical records of stage I NSCLC patients who undergone curative resection at Asan Medical Center between 2000 and 2009 were reviewed. Results: Total 940 patients with pathologically proven stage I NSCLC were included. Patients with lymphatic-type adenocarcinoma(LTA) were 74, other adenocarcinoma(ADC) 580, and squamous cell carcinoma(SCC) 246. Median length of follow-up was 62 months(3-138), median survival was 146 months, and median disease-free survival(DFS) was 199 months. During follow-up, recurrence occurred in 221 patients(23.5%). Incidence of recurrence was peaked within 2 years after resection, then gradually decreased thereafter. Incidence LTA(AIS/MA/IA) group was significantly rare(13.5%) throughout the all follow-up period(median DFI of 60months), and its distribution shows relatively even distribution. Comparing ADC and SCC, ADC seemed to show better 5-year OS in univariate analysis(p=0.003), but not in multivariate analysis. Furthermore, there were no significant difference in 5-year DFS(p=0.331). ADC shows higher proportion of distant metastasis, even though ADC group has lower T-stage. SCC shows higher incidence of local recurrence.

Keywords: lung, Adenocarcinoma, GGO, Surgery
Conclusion: Recurrence of ADC occurred within 2 years after resection, and shows higher proportion of distant metastasis (74.0% vs. 57.2%) even though ADC group has lower T-stage. Most of recurrence of both ADC and SCC groups were peaked within 2 years after resection. LTA group shows significantly delayed pattern of recurrence.

Keywords: recurrence, lung cancer

P1.05-039 RECURRENCE AND SURVIVAL OUTCOME AFTER SEGMENTECTOMY FOR NON-SMALL CELL LUNG CANCER: A LONG-TERM FOLLOW-UP STUDY AT A SINGLE INSTITUTE
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1Thoracic Surgery, Kumamoto University Hospital, Kumamoto/Japan, 2Division of Thoracic Surgery, Toronto General Hospital, Toronto/AB/Canada, 3Thoracic Surgery, Minami Kyushu Hospital, Aira/Japan, 4Department of Pathology and Experimental Medicine, Kumamoto University, Graduate School of Medical Sciences, Kumamoto/Japan

Background: This study aimed to investigate the factors associated with long-term outcomes of segmentectomy for non-small cell lung cancer (NSCLC) carried out at a single institute. Methods: 179 patients with stage I NSCLC who underwent a segmentectomy between 2005 and 2009 were investigated. Histological classification was reassessed according to the criteria of the 2015 WHO. Results: 179 patients with stage I NSCLC (159 adenocarcinomas (ADCs), 14 squamous cell carcinomas (SQCs), 4 adenosquamous carcinomas, and 2 typical carcinoids) who underwent segmentectomy between 2005 and 2009 were investigated. The mean follow-up was 73 months. The 5-year overall survival (OS) and 5-years disease-free survival (DFS) were 91.8% and 90.2%, respectively. Seven cases of distant recurrence and 8 local-regional recurrence occurred. Multivariate analysis revealed that lymphovascular invasion (LVI) was the independent predictor of recurrence (P=0.005) and survival (P=0.007). There was the independent predictor of 5-DFS (P=0.043, P<0.001). Among invasive ADC patients, micropapillary pattern (MIP) >5% was identified as an independent predictor of recurrence (P=0.005) and survival (P=0.007). There were five local recurrences in patients with MIP more than 5 years after segmentectomy.

Conclusion: LVI was an independent predictor of the recurrence and overall survival. In patients with invasive ADC, MIP>5% was a multivariable predictor of recurrence and overall survival. Among the patients who underwent a segmentectomy, 5 years without recurrence is not sufficient to conclude that patients with NSCLC is cured.

Keywords: non-small cell lung cancer, NSCLC, early stage, segmentectomy

P1.05-040 PROGNOSTIC FACTOR OF NODE INVOLVEMENT PATTERN IN COMPLETELY RESECTED PNI SQUAMOUS CELL CARCINOMA PATIENTS
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Background: In patients with non-small cell lung cancer, the degree of regional lymph node involvement is an important prognostic factor. The prognostic significance of lymph node involvement pattern is unclear in the seventh edition of TNM classification. Squamous cell carcinoma (SCC) often arises in the central way and directly invades intrapulmonary and hilar lymph nodes. In this study, we reviewed our population of operated SCC patients classified as pathologically N1 (pN1) to evaluate the association between N1 lymph node involvement patterns and the prognosis. Methods: From our institutional database of 3,264 consecutive patients underwent surgical resection for NSCLC at our hospital between January 1987 and December 2010, we examined 152 patients with completely resected pN1 squamous cell carcinoma. We performed reassessment of the data according to the seventh edition of TNM classification of lung cancer. We divided the patients into two groups based on lymph node involvement pattern; direct and separate pattern. The direct pattern was defined as lymph node metastasis by the primary tumor directly with continuity, separate pattern as metastasis without continuity. Survival curves were generated by the Kaplan-Meier method and multivariate analysis was based on the Cox proportional hazards model. Results: In the lymph nodes metastasis pattern, 75 (49%) patients were the direct group, 77 (51%) patients were the separate group. The percentage of sleeve lobectomy was significantly higher in the direct group and lobectomy without bronchoplastic procedure was higher in the separate group. The median follow-up period was 50 months. The 5-year survivals of the direct and separate group were 54% and 41% (p=0.01). The 5-year survival of patients with the direct group was as good as pN0 patients (p=0.78). No survival difference between the separate group and pN2 patients was noted (p=0.06). Overall recurrence rate of the direct group (44% (33/75)) was lower than the separate group (50% (39/77)), but there was no significant difference among them (p=0.09). No significant difference was noted in recurrence pattern (distant or locoregional) when comparing the direct group or separate group (p=0.27). Multivariate analyses of survival, lymph node involvement pattern (p=0.02) and lymphatic infiltration (p=0.02) was independent prognostic factor. Conclusion: Lymph node involvement pattern of patients with pN1 squamous cell carcinoma is significant prognostic factor. Survival of the direct pattern is higher than the separate pattern.

Keywords: lung cancer, Squamous cell carcinoma, lymph node involvement pattern, direct
Abstracts

P1.05-042 TREATMENT STRATEGY OF LIMITED SURGERY FOR EARLY LUNG CANCER
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Background: The standard surgical procedure for operable lung cancer is lobectomy with lymph node dissection. However early lung cancer cases have been increasing in Japan and they have been able to be candidates for limited operation. We have predicted early lung cancer depending on image findings and performed a limited operation positively.

Methods: We reviewed 124 patients who had undergone limited resection for early lung cancer by making full use of image findings.

Results: Of the 124 cases, 85 cases (69%) were limited resection. The predominant morphological cancer were Lepidic (n=70) and Acinar (n=32). The adjuvant strategies for early cancer on limited resection may inform adjuvant strategies.

Conclusion: A difference in survival can be seen between the three commonest adenocarcinoma subtypes (Acinar, Lepidic and Solid) at 1, 2 and 3 years following surgical resection. Interpreting results on other sub-types is limited by small numbers. Lepidic and Solid have the best and worst survival rates respectively. Limitations include a lack of adjustment for pathological stage or comorbidities and a lack of cancer-specific mortality data. Future studies may evaluate if the morphology of lung adenocarcinomas could have a role in defining adjuvant and surveillance strategies.

Keywords: NSCLC, Surgery, Adenocarcinoma, survival

POSTER SESSION 1: P1.05: EARLY STAGE NSCLC SURGERY – MONDAY, DECEMBER 5, 2016

P1.05-043 SURVIVAL FOLLOWING SURGICAL RESSECTION OF LUNG ADENOCARCINOMA STRATIFIED ACCORDING TO MORPHOLOGICAL SUB-TYPE
Haval Babata, Timothy Edwards, Charlene Tennyson, Philip Poden, Anshuman Chaturvedi, Philip Crossbe, Richard Boaton, Matthew Evison
University Hospitals of South Manchester, Manchester/United Kingdom

Background: Lung adenocarcinoma is the commonest histological sub-type of Non-small cell lung cancer (NSCLC) and a leading cause of death worldwide. Identifying factors that may influence survival or the risk of recurrence following resection of lung adenocarcinoma may inform adjuvant strategies and the intensity of surveillance programs. The aim of this study was to assess the effect of morphological sub-type on survival following surgical resection.

Methods: Patients who underwent surgical resection for non-small cell lung cancer between 2011 and 2016 at a tertiary thoracic surgical and lung cancer centre were identified from pathological records (n=1387). Patients with adenocarcinoma (n=705) were selected and the predominant morphological subtyping was recorded. Survival data was obtained from national death registers. Results: Of the 705 adenocarcinomas, Acinar (n=325), Lepidic (n=133) and Solid (n=333) were the most frequent histological subtypes identified. Numbers for other subtypes were small and therefore 3 year survival was not always possible to calculate.

Conclusion: A difference in survival can be seen between the three commonest adenocarcinoma subtypes (Acinar, Lepidic and Solid) at 1, 2 and 3 years following surgical resection. Interpreting results on other sub-types is limited by small numbers. Lepidic and Solid have the best and worst survival rates respectively. Limitations include a lack of adjustment for pathological stage or comorbidities and a lack of cancer-specific mortality data. Future studies may evaluate if the morphology of lung adenocarcinomas could have a role in defining adjuvant and surveillance strategies.

Keywords: limited resection, early lung cancer, segmentectomy, wide wedge resection
P1.05-045 ADJUVANT CHEMOTHERAPY FOR PATIENTS WITH STAGE IB NON SMALL CELL LUNG CANCER

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Background: The prognosis of stage Ib non-small cell lung cancer (NSCLC) remains poor, there’re much controversy over the necessity of adjuvant chemotherapy to them. The aim of this study is to investigate the clinical characters influencing prognosis of the stage Ib non-small cell lung cancer (NSCLC) and to explore the indication of postoperative chemotherapy.

Methods: In total, 569 stage IB patients with NSCLC who underwent surgical resection with or without adjuvant therapy were included in this study. Cox proportional-hazards ratios were used to identify independent prognostic factors for survival. Kaplan-Meier survival curves were calculated to estimate survival rates. Results: Adjuvant chemotherapy, tumor size and performance status were independent prognostic factors in the univariate and multivariate analyses. Patients with tumor greater than 4 cm and patients with good performance status benefitted from adjuvant chemotherapy. On the contrary, to the patients with tumor less or equal to 4 cm or patients without good performance status, giving adjuvant chemotherapy is not better than giving surgery alone.

Conclusion: Adjuvant chemotherapy, tumor size and performance status were closely correlated with survival in the stage Ib NSCLC, patients with tumor greater than 4 cm and patients with good performance status benefitted from adjuvant chemotherapy.

Keywords: lung cancer, adjuvant chemotherapy, stage IB

Figure 2 Survival curves for subset analysis. A. Survival according to adjuvant therapy in patients with tumor size greater than 4 cm. B. Survival according to the adjuvant therapy in patients with tumor size less than or equal to 4cm. C. Survival according to the adjuvant therapy in patients with good performance status. (Eastern Cooperative Oncology Group, 0) D. Survival according to the adjuvant therapy in patients with good performance status. (Eastern Cooperative Oncology Group, 1)
P1.05-046 RANDOMIZED STUDY OF ADJUVANT DOCETAXEL VS. OBSERVATION FOR COMPLETELY RESECTED STAGE IB-IIIA NSCLC WITH 11 YEARS’ MEDIAN FOLLOW-UP

Wen-Zhao Zhong,1 Xue-Ning Yang,1 Hong-Hong Yan,1 Ri-Qiang Liao,1 Qiang Nie,1 Song Dong,1 Ben-Yuan Jiang,1 Qing Zhou,1 Jin-Yi Yang,1 Yi Long Wu2
1Department of Pulmonary Oncology, Guangdong General Hospital & Guangdong Academy of Medical Sciences, Guangzhou/China, 2Guangdong Lung Cancer Institute, Guangdong General Hospital & Guangdong Academy of Medical Sciences, Guangzhou/China

Background: Although previous meta-analyses have verified the significance of adjuvant chemotherapy, the role of adjuvant carboplatin plus docetaxel(DC) among patients with completely resected NSCLC with long periods of follow-up remains unclear. Methods: Eligible patients were randomly assigned to cycles of DC or observation after complete resection. The primary end point was DFS; secondary ones were OS, the toxicity and safety of drugs. An increase of 15% in 1-year survival rate (observation arm 70%) with a sample size of 270 patients was considered significant. Results: This trial was suspended prematurely in June 2005 due to the negative survival benefits from chemotherapy in stage IB patients in the JBR10 trial. 82 patients were enrolled between 2005 to 2009(43 and 39 in each arm). Two arms were well-balanced on age, gender, histology, smoking history and staging. Median follow-up was 11 years(10.5-13y). DFS was marginally significantly longer in DC arm than observation (10.4 vs. 3.7y; HR=0.58; 95% CI, 0.33-0.93; P=0.06), as was 5-year DFS rates(63% vs. 41%; P=0.057). No statistical significance existed in OS (NR vs. 7y; P=0.103) or 5-year survival rates(76% vs. 61%; P=0.148). Multivariable analysis revealed patients receiving adjuvant DC(HR=0.54, 95% CI: 0.30-0.96, P=0.036) and with stage IB disease(HR=0.34, 95%CI: 0.19-0.61, P=0.001) bore lower recurrence risk. In DC arm, 84% of patients received at least one cycle of DC, and 53% of patients finished four. Grades 3 adverse events occurred in 5%/2/4 patients in chemotherapy group. The time-varying endpoints showed adjuvant DC could delay the recurrence and mortality in the first postoperative 5y, while two arms tended to be equivalent after 5y.

Conclusion: This is the first randomized trial used DC as adjuvant chemotherapy suggesting a potentially significant role for completely resected early stage NSCLC with safety and compliance. Additionally, at least 10y’s follow-up for each patient was vital to investigate the long-term time-varying recurrence and mortality pattern.

Keywords: docetaxel, carboplatin, non-small cell lung cancer, adjuvant chemotherapy

Table. Multivariable analysis

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<th>Variable</th>
<th>OR (95% CI)</th>
<th>P-value</th>
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</thead>
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<td>Age</td>
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<tr>
<td>&lt;50</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>51-60</td>
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<tr>
<td>61-70</td>
<td>1.33 (0.91-1.95)</td>
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<td>71-80</td>
<td>1.59 (1.06-2.38)</td>
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</tr>
<tr>
<td>&gt;80</td>
<td>2.27 (1.29-3.98)</td>
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</tr>
<tr>
<td>Female</td>
<td>0.70 (0.55-0.82)</td>
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<td></td>
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<tr>
<td>0</td>
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<tr>
<td>1</td>
<td>1.13 (0.95-1.34)</td>
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</tr>
<tr>
<td>2</td>
<td>1.58 (1.26-1.98)</td>
<td>&lt;0.001</td>
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<td>Sub-lobar</td>
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<tr>
<td>Lobectomy</td>
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<td>Pneumonectomy</td>
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</tr>
<tr>
<td>Yes</td>
<td>1.54 (1.20-1.99)</td>
<td>0.001</td>
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</tbody>
</table>

Keywords: non-small cell lung cancer, adjuvant chemotherapy

P1.05-047 EARLY MORTALITY IN PATIENTS WITH NON-SMALL CELL LUNG CANCER UNDERGOING ADJUVANT CHEMOTHERAPY

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Background: Although adjuvant chemotherapy improves survival in patients with completely resected non-small-cell lung cancer (NSCLC) compared to surgery alone, it is also associated with potentially disabling or lethal adverse events. Since there is limited information on the early mortality among patients undergoing adjuvant chemotherapy, we used the National Cancer Data Base (NCDB) to calculate the percentage of deaths within the first 6 months from starting chemotherapy. Methods: The NCDB was queried for patients aged 18 or older, diagnosed with stage IB to IIIA NSCLC (AJCC 7th edition) from 2004 to 2012, who underwent surgery with negative margins followed by multi-agent chemotherapy, starting within 120 days from the surgical resection. Patients who received radiation therapy were excluded. Age groups were divided into <50, 51-60, 61-70, 71-80 and >80 years. Early mortality from months 1 to 6 were calculated and multivariate logistic regression was performed to identify clinical variables independently associated with mortality at six months from the date of initiation of adjuvant chemotherapy. Results: A total of 19,731 patients met the eligibility criteria. The median age was 65 (range 19-89). The percentage of deaths at 1, 2, 3, 4, 5 and 6 months were 0.6%, 1.3%, 1.9%, 2.6%, 3.3% and 4.2% respectively. The percentages of death at 6 months for each age group from <50 years to >80 years were 2.7%, 3.2%, 4.1%, 5.3% and 7.8% respectively. Factors independently associated with increased 6-month mortality included increased age, male gender, higher Charlson-Deyo co-morbidity score (CDCS), type of surgery, length of stay (LoS) >6 days and 30-day readmission (Table). Conclusion: There is a high risk for early mortality among patients undergoing adjuvant chemotherapy for NSCLC, particularly in patients older than 70, with high co-morbidity score and a more complicated post-operative period.

POSTER SESSION 1: P1.05: EARLY STAGE NSCLC
NEOADJUVANT AND ADJUVANT CHEMOTHERAPY – MONDAY, DECEMBER 5, 2016

POSTER SESSION 1: P1.05: EARLY STAGE NSCLC
NEOADJUVANT AND ADJUVANT CHEMOTHERAPY – MONDAY, DECEMBER 5, 2016
Background: Although the complete surgical resection in most cases of the non-small cell lung carcinoma with N1 involvement is feasible, a considerable number of patients develop recurrence and the disease course is highly variable. Timing and pattern of recurrence are essential to explain strong prognostic heterogeneity, however, research focusing on these subjects has rarely been reported. We investigated the patterns of recurrences and event rates over time in patients with completely resected N1-stagell lung adenocarcinoma. Methods: We retrospectively reviewed the medical records of 60 consecutive patients who underwent a complete surgical resection for N1-stage II lung adenocarcinoma. Survival curves were generated using the Kaplan-Meier method, and the event dynamics was estimated using the hazard function. Results: The median recurrence-free survival was 36.8 months. The life table survival analysis showed that the 1-year, 3-year and 5-year recurrence free survival rates were 85.1%, 50.2% and 36.6%, respectively. Approximately 15 (42.2%) patients experienced recurrence, and the patterns of recurrences included loco-regional in 41 patients (27.2%), distant in 68 (65.0%), and both in 42 (27.8%). Most commonly involved organs were the lung (n=77, 47.0%), followed by lymph nodes (n=41, 27.2%), bone (n=31, 20.5%), and brain (n=30, 19.9%). There were 228 patients who received adjuvant chemotherapy. Patients treated with adjuvant chemotherapy showed better recurrence-free survival (chemotherapy group vs non-chemotherapy group; median survival 42.5 months vs 25.4 months), and post-recurrence survival (chemotherapy group vs non-chemotherapy group; median survival 39.8 months vs 22.6 months) compared to those of patients without adjuvant chemotherapy. The multivariate analysis revealed that adjuvant chemotherapy was significantly correlated with recurrence-free survival (p=0.004) and post recurrence survival (p=0.001). Patients who underwent adjuvant chemotherapy had less distant (p=0.045) and less lung (p=0.005) recurrence, while there is no difference in loco-regional (p=0.837) and brain (p=0.997) recurrence. The recurrence hazard curve demonstrated similarly shaped and sized initial and second peak at 16 and 24 months, followed by a smaller peak at 40 months. The temporal distribution of the recurrence risk varied depending on adjuvant chemotherapy. A visual inspection of the hazard curves suggested that the patients without adjuvant chemotherapy exhibited earlier and higher first peaks with higher hazard rate over time. Conclusion: In the patients who underwent completely resected N1-stagell lung adenocarcinoma, adjuvant chemotherapy not only reduced the recurrence hazard, but also delayed the recurrence, altered pattern of recurrence and improved post-recurrence survival.

Keywords: recurrence dynamics, recurrence pattern, N1 adenocarcinoma, adjuvant chemotherapy

P1.05-049 NEOADJUVANT ERLOTINIB TREATMENT IN PATIENTS WITH RESECTABLE NON-SMALL CELL LUNG CARCINOMA
Matthijs Van Gool, Houke Klomp
NKI-AVL, Amsterdam/Netherlands

Background: The value of neo-adjuvant therapy in patients with resectable non-small cell lung carcinoma (NSCLC) is limited. Recent advances in targeted therapy have provided novel treatment options for NSCLC with promising results. The Epidermal Growth Factor Receptor (EGFR) is over expressed or may harbour activating mutations in adenocarcinoma in particular. Inhibition of EGFR with tyrosine-kinase inhibitor (TKI) therapy has a favourable outcome in advanced stage patients with activating mutations. The purpose of this study was to prospectively evaluate 18F-FDG-PET/CT metabolic response to neo-adjuvant erlotinib, in patients with resectable NSCLC. Methods: This study was designed as a multicentre open-label phase II trial, performed in the Netherlands. Patients received preoperative erlotinib 150 mg once daily for 3 weeks. Metabolic response evaluation was performed using FDG-PET/CT scan. Tumour FDG uptake and changes were measured by standardized uptake values (SUV). Metabolic response was classified using EORTC criteria. Metabolic response was compared to the histopathological response and survival. Results: From December 2006 until November 2010, 60 patients were enrolled in this study. In 43 patients (18 male, 25 female), FDG-PET/CT scans and histopathologic response monitoring were available. 14 patients (33%) showed a metabolic response. Histopathologic examination showed a response in 13 patients (30%). In predicting histopathologic response, FDG-PET/CT showed an area under the curve of 72%. Metabolic responders show an improved overall and progression free survival in comparison to patients without metabolic response.

Conclusion: FDG-PET/CT may be used as a predictive tool to identify patients with advantage of neo-adjuvant EGFR-TKI treatment in resectable NSCLC.

Keywords: neo-adjuvant, Surgery, EGFR-TKI
**Abstracts**

**POSTER SESSION 1: P1.05: EARLY STAGE NSCLC NEOADJUVANT AND ADJUVANT CHEMOTHERAPY - MONDAY, DECEMBER 5, 2016**

**P1.05-051 SAFETY AND COMPLIANCE DATA OF THE PHASE III STUDY OF ADJUVANT CHEMOTHERAPY IN COMpletely RESECTED P-STAGE I NON SMALL CELL LUNG CANCER: JCOG0707**

Hideo Kunitoh, Hiroyuki Sakurai, Masahiro Tsuibo, Masashi Wakabayashi, Morihito Okada, Kenji Suzuki, Norihiko Ikeda, Mitsuhiro Takenyumai, Yasuhisa Ohide, Makoto Takahama, Katsuji Yoshida, Isao Matsumoto, Motohiro Yamashita, Takashi Marutsuka, Hiroi Date, Yasaki Saito, Yosihide Yamashita, Narihito Okumura, Shin-Ichi Watanabe, Hisao Asamura

Background: Post-operative UFT (tegafur/uracil) has been shown to prolong survival of Japanese patients (pts) with completely resected, pathological (p) stage I (T1b 2 cm) non small cell lung cancer (NSCLC). This trial aimed at estimating the efficacy of S-1 (tegafur/gimeracil/oteracil) compared to UFT as adjuvant therapy in this population. Methods: Eligible pts had undergone complete resection with lymph node dissection for p-stage I (T1N2M0, T1b 2 cm, by 5th Edition UICC TNM) NSCLC, within 56 days of enrollment. Pts were randomized to receive either oral UFT 250mg/M2/d for 2 years (Arm A), or oral S-1 80mg/M2/d for 2 weeks followed by 1 week of rest, for 1 year (Arm B). The primary endpoint was overall survival (OS). Based upon the results of monitoring in Jun. 2013, which showed the combined OS of the 2 arms better than expected (4-year OS of 91.6% vs. presumed 5-year OS of 70-76.5%), the study was judged to be underpowered. The study protocol was reanalyzed based on the new classifications of T category (Table 1).

**Conclusion:** UFT tended to improve survival in each T category defined by TNM (except for T1b, when compared to surgery alone).

Keywords: tegafur/uracil, lung adenocarcinoma, TNM Classification, postoperative adjuvant chemotherapy

**POSTER SESSION 1: P1.05: EARLY STAGE NSCLC NEOADJUVANT AND ADJUVANT CHEMOTHERAPY - MONDAY, DECEMBER 5, 2016**

**P1.05-053 IMPACT OF GENDER DIFFERENCE ON ADJUVANT CHEMOTHERAPY AFTER RADICAL RESECTION IN PATIENTS WITH NON-SMALL CELL LUNG CANCER**

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Background: Gender was an important prognostic factor in patients with advanced non-small cell lung cancer (NSCLC). However, there are few studies reporting the impact of gender difference on the efficacy of adjuvant chemotherapy (ACT) in NSCLC patients. Methods: 900 patients (584 men and 316 women) who received post-operative ACT in the Cancer Hospital of the Chinese Academy of Medical Sciences between 2001 and 2013 with complete records in the database of the hospital were analyzed in this study for analysis. The primary end point was disease-free survival (DFS) terms of gender. Survival analysis was performed using Kaplan–Meier estimates, log-rank tests and Cox’s proportional hazards regression analysis. Propensity score matching (PSM) was used, and survival analysis of the match data were carried out. Results: There was no significant difference in DFS between the two groups in terms of gender before propensity score was matched (105.857 weeks [95%CI 86.699, 125.015] vs. 95.714 months [95%CI 81.905, 109.523], P=0.575). Furthermore, no significant impact of gender on DFS was observed between the PS-matched groups (202.429 weeks [95%CI 208.078, 227.799] vs. 199.143 weeks [95%CI 66.539, 131.746], P=0.893). Conclusion: The results suggest that gender was not a prognostic factor on ACT after radical resected NSCLC. However, these conclusions are limited by the nature of this
Background: Adjuvant chemotherapy (AC) is recommended in patients (pts) with stage IB (tumour of >4 cm in diameter), IIA, IIB, and IIIA of non-small cell lung cancer (NSCLC) after complete resection. According to metaanalyses it prolongs survival of pts in good PS and age less than 75 years. The selection of pts for AC is hampered by the limited prof of possible toxic effects and the lack of predictive biomarkers. There are only few retrospective studies describing routine utilization of AC in specified areas. Presented AC uptake in stages II and III varies from 20% to 24% in Canada and USA. Methods: A retrospective study of AC uptake in pts with NSCLC from a Moravian region with 600,000 inhabitants was conducted, evaluation period was 2006-2013. Treatment strategy of all patients was discussed by surgeons and pneumo-oncologists on the interdisciplinary tumour boards before and after surgery. Uptake and compliance of AC was evaluated according to age, sex, TNM stages, type of surgery and other cofactors. AC was given in regimens using doublets of platinum with vinorelbine (rare gemcitabine or paclitaxel). Vinorelbine was applied both intravenously (25 mg/m²) and orally (60 - 80 mg/m²). The choice of cisplatin (80mg/m²) or carboplatin (AUC 5) was based on patient preference, PS and comorbidities. Results: Out of all 1557 pts with lung cancer, NSCLC was present in 1293 pts. 308 pts underwent curative-intent surgery and complete resection was achieved in 295 pts. 226 pts were pts with stage IB (tumour of >4 cm in diameter). The risk of recurrence should be considered especially in patients with NSCLC after complete resection. Methods: Four hundred and seventy-three consecutive lung adenocarcinoma patients who underwent surgical resection for pathological N0M0 disease, between January 2007 and December 2013, were retrospectively reviewed. The prognostic significance of EGFR mutations as oncogenic driver mutations in early-stage lung adenocarcinoma has yet to be determined. We aimed to evaluate the oncological significance of EGFR mutations in early-stage lung adenocarcinoma Methods: Four hundred and seventy-three consecutive lung adenocarcinoma patients who underwent surgical resection for pathological N0M0 disease, between January 2007 and December 2013, were retrospectively reviewed. The prognostic significance of EGFR mutation status was evaluated in 407 cases from these patients. Overall survival (OS) and recurrence-free interval (RFI) curves were estimated using the Kaplan-Meier method and compared using a log-rank test. Univariate and multivariate analyses were performed using a Cox proportional hazards model. Results: There was no statistical significance in the 5-year OS (89.3 vs. 95.3%, P = 0.20, HR = 1.605) or RFI (86.5 vs. 93.5%, P = 0.6, HR = 1.956) rates between the EGFR-positive (n=183) and EGFR-negative (n=224) groups. Considering the risk of recurrence and positive EGFR mutation status, OS and RFI rates were subsequently calculated among specific histological subtypes. After adenocarcinoma in situ (AIS), minimally invasive adenocarcinoma (MIA), and invasive mucinous adenocarcinoma (IMA) cases were excluded, all analysed cases were ≤5.0 cm in tumour diameter and were classified as pathological Stage IA-IB. Among specific histological subtypes, the 5-year RFI (81.5 vs. 92.4%, P = 0.04, HR = 2.160) but not OS (86.8 vs. 94.3%, P = 0.31, HR = 1.499) was significantly poorer in EGFR-positive cases compared to EGFR-negative cases. Univariate analysis, excluding AIS, MIA, and IMA, identified a pathological tumour size of ≥3.0 cm, a highly malignant subtype (micropapillary or solid predominant adenocarcinoma), a low lymphatic/vascular invasion, and a positive EGFR mutation status as significant positive predictive factors for RFI. Multivariate analysis confirmed pleural invasion and a positive EGFR mutation status as independent positive predictive factors for RFI. Conclusion: EGFR mutation status is a predictive factor for postoperative recurrence in early-stage lung adenocarcinoma, with the exception of AIS, MIA, and IMA. The risk of recurrence should be considered with EGFR mutation status and predominant histological subtype in resected early-stage lung adenocarcinoma patients. Keywords: Early-stage, Surgery, EGFR, Adenocarcinoma of these patients were reviewed carefully. The median age was 66.4 years with 512 stage IA and 281 stage IB. Histopathologically, there were 590 adenocarcinoma, 150 squamous cell carcinoma, 32 large cell carcinoma, and 21 other histology cases. (Surgical procedure was segmentectomy, lobectomy, and pneumonectomy for 46, 588, and 8 patients, respectively. Clinico-pathological factors such as smoking history, histology, pathological vascular invasion (v), and lymphatic vessel invasion (ly) were analyzed. Results: Recurrence occurred in 132 cases. Multivariate analysis showed that T factor, v(+) and/or ly(+) had statistical significance with recurrence n P1a and T2a cases, there were no statistical significance between recurrence and pathological ly(+) and/or v(+). But only in T1b cases, ly(+) or v(+) or both had statistical significance with recurrence. Conclusion: We identified that T factor, v(+), and smoking history were predictive factors for recurrence in stage IA and IB NSCLC patients. Because of good prognosis, pT1b patients whose both v and ly were negative may not take UFT as adjuvant chemotherapy. Keywords: NSCLC, stage IA and stage IB, recurrence
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**Background:** Although surgical resection remains the optimal treatment for early-stage NSCLC, up to 50% of patients with stage I and II relapse within 5 years after curative resection. Therefore, prognostic markers are important as these patients might benefit from adjuvant therapy. The goal of this study was to evaluate established PET quantification metrics including: maximal standard uptake volume (SUVmax), metabolic tumor volume (MTV) and total lesion glycolysis (TLG) as prognostic markers for early recurrence and overall survival in resected early stage lung cancer. Methods: Between January 2003 and December 2010, 182 surgically resected patients with stage I-II NSCLC who underwent 18F FDG PET/CT less than one month prior to surgery were evaluated. All patients had at least 5 years of follow-up. Cox proportional hazard model was used to determine the association between baseline variables and survival respectively time to recurrence. For the multivariate analysis the following variables have been included: tumor size on CT, age, tumor stage, histology, SUVmax, TLG (for TLG2.5, threshold at 42% SUVmax) and TLG2.5 (cut-off at SUV 2.5) and MTV2.5 (for MTV2.5, threshold at 42% 2.5). To identify high-risk patients we used survival trees. Results: 133 patients were included, 71 with adenocarcinoma, 62 with squamous cell carcinoma. TLG2.5 and MTV2.5 values have been a significant prognostic factor for recurrence (P<0.0001). Patients with a MTV2.5 above 42 cm3 have been a significant prognostic factor for recurrence (P<0.0001). Patients with a MTV2.5 within one year might be identified and adjuvant therapy following surgical resection could improve outcome for those patients.

**Keywords:** prognostic marker, PET-CT, Thoracic Surgery, early stage NSCLC

**Poster Session 1 • P1.05: Early Stage NSCLC Recurrence – Monday, December 5, 2016**

**P1.05-058 Prognostic Factors of Post-Recurrence Survival in Resected Stage I Non-Small Cell Lung Cancer**

Yasuki Kuchibuchi, Yoshiteru Kidokoro, Takashi Oono, Yohei Yurugi, Makoto Wakahara, Ken Miwa, Kunio Araki, Yuji Taniguchi, Hiroshige Nakamura

**Background:** After surgical resection is a major obstacle in the cure and long-term survival, and has become the most common cause of death. Knowledge of post-recurrence factors and efficacy of the therapy after recurrence remain controversial. We evaluated the prognostic factors of post-recurrence survival (PRS) in patients of resected stage I NSCLC. Methods: Of the 551 patients who underwent a complete resection for stage I NSCLC between 2005 and 2013, 89 (16.2%) patients who experienced recurrence were selected for this retrospective study. Case of preoperative therapy and death within 30 days of operation were excluded. Clinicopathological factors were analyzed for PRS by univariate and multivariate analyses. Univariate and multivariate analyses were performed by using the Cox proportional hazards model. Results: 89 patients experienced recurrence during a median follow-up period of 54.0 months. The median recurrence free interval (RFI) was 16.0 months. The 1-year RFS and 3-year RFS were 65.6% and 44.7%, respectively. The pattern of recurrence was loco-regional in 24(27.0%), and distant in 65(73.0%). The most common orgin site of recurrences were contralateral lung in 42 patients, the ipsilateral thorax in 24, bone in 24, brain in 12, in 19. Univariate analysis indicated that male sex (p=0.035), smoking history (p=0.034), larger tumor size over 25mm (p=0.008), stage IB (p=0.044), squamous cell carcinoma (p=0.001), RFI within 16 months (p=0.011), presence of symptoms (p=0.001), bone metastasis (p=0.001), liver metastasis (p=0.009) and not having received any treatment (p=0.001) were significant prognostic factors of worse PRS. Multivariate analysis revealed that larger tumor size over 25mm (p=0.05), RFI within 16 months (p=0.05) and no treatment for recurrence (p=0.001) were the independent prognostic factors for poor PRS. The result of multivariate analysis of PRS indicated that post-recurrence therapy had a strong impact on PRS. Therefore, we further examined PRS in 61 patients who underwent any post-recurrence therapy. For patients receiving treatment for recurrence, bone metastasis (p=0.042) was a significant predictive factor of worse PRS, while treatment with EGFR TKIs (p=0.045) was a good prognostic factor. Conclusion: This study showed that tumor size, RFI, and post-recurrence therapy were prognostic factors for PRS. In the patients who underwent treatment for recurrence, bone metastasis and treatment with EGFR TKIs were independent prognostic factors. Although further validation is needed, this information is important for future design of clinical trials for therapy after recurrence.

**Keywords:** NSCLC, prognostic factor, Surgery, post-recurrence therapy

**Poster Session 1 • P1.05: Early Stage NSCLC Recurrence – Monday, December 5, 2016**

**P1.05-059 Factors Associated with Recurrence and Survival in Patients with Curatively Resected Stage IIA Adenocarcinoma of the Lung**

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**Background:** Even when meticulously clinically and pathologically studied, completely resected stage IIA adenocarcinoma of the lung does recur. However, there are few data regarding the patterns of recurrences and their risk factors in this population. Therefore, this study characterizes cancer recurrence and its risks and assesses recurrence-free survival in patients with curatively resected stage IIA adenocarcinoma. Methods: Between January 1990 and December 2005, a total of 214 patients were given a final diagnosis of pathologic stage IA (UICC-7) adenocarcinoma of the lung. The medical records of these patients were retrospectively reviewed with regard to patient characteristics, tumor pathologic findings and follow up status. Survival was analyzed by the Kaplan-Meier method, log-rank test, and Cox proportional hazards analysis. Results: The median follow up after curative resection was 83 months. Cancer recurred in 28 patients (13%). Among them, local recurrence occurred in 10 patients (5%), whereas distant recurrence occurred in 18 patients (8%). Recurrence earlier and later than 5 years after surgery was in 15 patients (7%) and in 13 patients (6%), respectively, with nearly constant risk. At 5 years after index recurrence, 175 patients (82%) were alive without evidence of cancer recurrence, 11 patients (8%) had experienced recurrence of cancer but still alive and 11 patients (5%) had died with non-cancer causes. Recurrence-free 5- and 10-year survival rates were 92.5 and 70.8%, respectively. Univariate analysis revealed five significant prognostic factors: gender (p=0.0177); lepidic component (p=0.0007); tumor location (p=0.0099); pleural invasion (p=0.0274) and lymphatic or vascular vessel invasion (LVI) (p=0.0001). Multivariate analysis revealed lepidic component, tumor location, and LVI as significant factors. Hazard ratios for recurrence were 0.381 for having lepidic component (95% CI, 0.147-0.979; p=0.0451), 0.361 for right sided tumor (95% CI, 0.188-0.692; p=0.0022), and 2.785 for having LVI (95% CI, 1.392-5.55; p=0.0038). Conclusion: Surgically "cured" stage IIA adenocarcinoma of the lung recurs. Our analyses indicate no-lepidic component, tumor location, LVI as an independent indicator for cancer recurrence. Identifying high-risk patients for recurrence will simplify decision making for postoperative treatment strategies.

**Keywords:** recurrence, adenocarcinoma of the lung, lymphovascular invasion, p-stage IA

**Poster Session 1 • P1.05: Early Stage NSCLC Miscellaneous – Monday, December 5, 2016**

**P1.05-060 Adherence to Surveillance Guidelines in Resected NSCLC: Physician Compliance and Impact on Outcomes**

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**Background:** Guidelines on resected NSCLC have varying recommendations for appropriate post-operative surveillance. There is general consensus that patients require follow up q6m with clinic visits or CT scans for the first 2 y. This study evaluated compliance with surveillance guidelines and the impact on outcomes. Methods: The BC Cancer Agency provides comprehensive cancer control for a population of 4.5 million. Inclusion criteria included referred patients from 2005-2010, resected stage Ib/Ii NSCLC, minimum 2 y (f/u) at the BCCA, no prior lung cancer diagnosis. Retrospective chart review collected baseline parameters, follow up visits, CT imaging, recurrence and death. Results: 479 were referred and 263 were eligible. Baseline characteristics median age 68, male 52%, current/former/never smoker 38/52/10%, stage...
P1.05-062 IS LUNG MICROWAVE THERMOABLATION A VALID ALTERNATIVE TO SURGERY IN HIGH-RISK PATIENTS? A PROPENSITY MATCH ANALYSIS

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Background: Surgery is considered the best treatment in Stage I non-small cell lung cancer. Local non-surgical therapies (radiotherapy, thermoablation) are becoming valid alternative to surgery in high risk patients (poor cardiac or pulmonary function, elderly patients). Methods: Patients submitted in our Department to Microwave thermoablation (MW) were compared with a cohort of patients submitted to lung lobectomy in the same period of time, abstracted from our database with a propensity match method. The study was retrospective on data recorded prospectively. Primary endpoint was overall survival. Results: From June 2009 to October 2014 in our Department, 36 patients underwent MW for Stage I non-small cell lung cancer (NSCLC) or lung metastasis. From our database were abstracted 41 patients with a propensity match method, submitted to lung lobectomy. Two groups were comparable by age, diagnosis, stage and gender. MW group resulted in a significant younger than Surgery group (75.5 vs 72.2 years; p<0.001). Lesion diameter was greater in MW group (20.9 vs 26.5 cm; p<0.001). Overall survival, analyzed by actuarial survival curve, was comparable (Logrank test p=0.2). Conclusion: In our experience, in a propensity match evaluation, lung MW thermoablation is confirmed as a valid alternative treatment in high risk patients. Randomized prospective studies are mandatory.

Keywords: Microwave; Thermoablation; Lobectomy

P1.05-063 MULTICENTER OBSERVATIONAL STUDY OF PATIENTS WITH RESECTED EARLY-STAGED NSCLC, WHO WERE EXCLUDED FROM AN ADJUVANT CHEMOTHERAPY TRIAL

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Background: Treatment options for early-stage non-small cell lung cancer (ES-NSCLC) are generally well-tolerated. Minimally-invasive surgical techniques, stereotactic ablative radiotherapy (SABR) and radiofrequency ablation (RFA) can all achieve post-treatment mortality of 0% in clinical trial settings. There has been increasing evidence to suggest that patients with interstitial lung disease (ILD) suffer severe toxicity after treatment for NSCLC. Treatment-related toxicity may result in death and may take the form of acute exacerbations of existing ILD following surgery or RFA, or severe radiation pneumonitis following SABR. Methods: We performed a systematic review of literature in compliance with PRISMA guidelines to investigate the rate of treatment-related toxicity and mortality following treatment for ES-NSCLC. The Medline and EMBASE databases were queried from respective dates of inception to January 2016. Treatment modalities included in the search strategy were surgery, SABR, RFA, particle beam therapy and conventionally-fractionated radiotherapy. Results were summarized with weighted statistics according to the sample size of individual studies. Results: A total of 3,054 unique records were screened and 282 full texts were reviewed. Forty-nine journal articles were included in the final analysis, with 92% of studies being retrospective in design. Thirty surgical studies with 1,716 patients, 13 SABR studies with 122 patients, 3 RFA studies with 46 patients, 2 proton beam therapy (PBT) studies with 7 patients and one carbon ion beam therapy (CIBT) study with 5 patients were included. Most patients in non-surgical studies were medically inoperable. Treatment-related or 30-day post-operative mortality was 2.3%, 15.5%, 8.7%, 5.8% and 0%, respectively, for surgery, SABR, RFA, PBT and CIBT. Treatment-related acute exacerbation of ILD or radiation pneumonitis was grade 3 was 12%, 25%, 25%, 12.5% and 20%, respectively. For patients treated with surgery, 5-year overall survival (OS) was 31.4% to 61.6% (median 54.2%) for patients with ILD and 70.5% to 88.3% (median 83.0%) for patients without ILD. For medically inoperable patients treated with SABR, 2 to 3-year OS was 0% to 53.8% (median 48.8%) for patients with ILD and 54% to 86.7% (median 70.8%) for patients without ILD. Studies that included only patients with idiopathic pulmonary fibrosis reported higher treatment-related toxicity compared to other studies. Conclusion: An elevated level of treatment-related toxicity is observed in patients treated for ES-NSCLC with co-existing ILD. Medically inoperable patients experienced high levels of treatment-related mortality. For surgery and SABR, overall survival was worse for patients with ILD compared to those without ILD.

Keywords: interstitial lung disease, Surgery, stereotactic ablative radiation therapy, non-small cell lung cancer

P1.05-061 INCREASED TREATMENT-RELATED TOXICITY IN PATIENTS WITH EARLY-STAGE NON-SMALL CELL LUNG CANCER AND CO-EXISTING INTERSTITIAL LUNG DISEASE

Hanbo Chen, Alexander Louie, Esther nossent, Gabe Boldt, David Palma, Suresh Senan

Background: Treatment options for early-stage non-small cell lung cancer (ES-NSCLC) are generally well-tolerated. Minimally-invasive surgical techniques, stereotactic ablative radiotherapy (SABR) and radiofrequency ablation (RFA) can all achieve post-treatment mortality of 0% in clinical trial settings. There has been increasing evidence to suggest that patients with interstitial lung disease (ILD) suffer severe toxicity after treatment for NSCLC. Treatment-related toxicity may result in death and may take the form of acute exacerbations of existing ILD following surgery or RFA, or severe radiation pneumonitis following SABR. Methods: We performed a systematic review of literature in compliance with PRISMA guidelines to investigate the rate of treatment-related toxicity and mortality following treatment for ES-NSCLC. The Medline and EMBASE databases were queried from respective dates of inception to January 2016. Treatment modalities included in the search strategy were surgery, SABR, RFA, particle beam therapy and conventionally-fractionated radiotherapy. Results were summarized with weighted statistics according to the sample size of individual studies. Results: A total of 3,054 unique records were screened and 282 full texts were reviewed. Forty-nine journal articles were included in the final analysis, with 92% of studies being retrospective in design. Thirty surgical studies with 1,716 patients, 13 SABR studies with 122 patients, 3 RFA studies with 46 patients, 2 proton beam therapy (PBT) studies with 7 patients and one carbon ion beam therapy (CIBT) study with 5 patients were included. Most patients in non-surgical studies were medically inoperable. Treatment-related or 30-day post-operative mortality was 2.3%, 15.5%, 8.7%, 5.8% and 0%, respectively, for surgery, SABR, RFA, PBT and CIBT. Treatment-related acute exacerbation of ILD or radiation pneumonitis was grade 3 was 12%, 25%, 25%, 12.5% and 20%, respectively. For patients treated with surgery, 5-year overall survival (OS) was 31.4% to 61.6% (median 54.2%) for patients with ILD and 70.5% to 88.3% (median 83.0%) for patients without ILD. For medically inoperable patients treated with SABR, 2 to 3-year OS was 0% to 53.8% (median 48.8%) for patients with ILD and 54% to 86.7% (median 70.8%) for patients without ILD. Studies that included only patients with idiopathic pulmonary fibrosis reported higher treatment-related toxicity compared to other studies. Conclusion: An elevated level of treatment-related toxicity is observed in patients treated for ES-NSCLC with co-existing ILD. Medically inoperable patients experienced high levels of treatment-related mortality. For surgery and SABR, overall survival was worse for patients with ILD compared to those without ILD.

Keywords: interstitial lung disease, Surgery, stereotactic ablative radiation therapy, non-small cell lung cancer

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Background: From Nov. 2008 to Dec. 2013, the Japan Clinical Oncology Group (JCOG) conducted a randomized phase III trial (JCOG0707), which compared the survival benefit of UFT and S-1 for completely resected pathological (p-) stage I and II NSCLC in the 6th TNM classification (NSCLC) and a total of 963 patients were enrolled. Recently, there is a growing concern that those who participated in clinical trials are highly selected and do not represent the “real-world” population. Hereby, we conducted a multicenter observational study of patients excluded from JCOG0707 trial during the study period. Methods: We retrospectively collected and analyzed the patients’ background, tumor profiles, post-surgical treatment of the patients who underwent R0 resection of p-stage (T1+2xcm and T2 in the 6th TNM classification) NSCLC and a total of 963 patients were enrolled. Results: Of the 48 institutions which took part in JCOG0707, 34 (enrolling 917 or 95.2% of all JCOG0707 patients) participated in this multicenter study, and 5062 patients were enrolled. Among them, 1627 (32.3%) patients fulfilled the eligibility criteria, but were not enrolled to JCOG0707 mainly due to patients’ decline (69.2%), or physicians’ discretion (20.5%). The accrual rate to JCOG0707 was various by institutions (4.1 to 64.1%), but was 25.9% (S1 (517/2016)) and 75.4% (S4 (917/1201)) in JCOG0707 (p < 0.001). Conclusion: Only selected population of candidate patients each institution did not correlate the accrual rate (R2=0.03 and 0.46). In the remaining 2389 (67.7%) patients, main ineligible reasons included the existence of active multiple cancer (29.1%), physicians’ decision based on the patients’ comorbidities (19.4%), delayed recovery from surgery (14.1%), and high age (age > 80 years) (10.7%). Majority of patients received no adjuvant chemotherapy (n = 3338, 66.7%). This proportion differed according to p-stage (T1: 75.3% vs. T2: 57.8%, p < 0.001) and the JCOG0707 eligibility (ineligible population: 77.6% vs. eligible population: 56.7%, p < 0.001). Standard UFT and s-1 were given in 31.0% and 21.0% of eligible patient respectively. Among those who received adjuvant UFT, 971 (62.6%) took UFT for one year or longer. Conclusion: Only selected population of candidate patients, even if they met the eligibility criteria, were enrolled to JCOG0707 for one year or longer. Further analysis of this “excluded” population, including long-term survival, is needed, this study might indicate that there is no need for a CT scan as additional surveillance no consensus has derived yet. The aim of this study was to further establish the appropriate follow-up modality: chest radiography with or without a computed tomography (CT) scan. Methods: In this retrospective study all patients diagnosed with a recurrence of previously treated stage I and II NSCLC between 2008 and 2016 at St Antonius Hospital, Nieuwegein the Netherlands, were included. We categorized patients after treatment in two imaging modality groups: one group received only chest radiographs (CR group) and the other group received one thoracic CT scan (CT group). The overall survival (OS), 1- and 3-years survival and progression free survival (PFS) were compared between the groups by using the Kaplan-Meier survival, the log rank-test and the Cox proportional hazard model. Results: 73 patients were enrolled, 50 patients in the CR group and 23 patients in the CT group. The median overall survival was 22.1 months (interquartile range (IQR) = 14.2-24.9 months) in the CR group compared to 27.2 months (IQR= 18.5-53.2 months) in the CT group (p = 0.12). After adjustment for the Eastern Cooperative Oncology Group (ECOG) performance score and morphologic features as explanatory factors, both the overall survival (hazard ratio (HR) = 1.43, 95% confidence interval (CI) = 0.76-2.70, p = 0.27) and the progression free survival (HR = 1.16, 95%CI = 0.65 - 2.07, p = 0.63) were not different in the CR group compared to patients in the CT group. There was no significant difference in the 1- and 3-years survival either. The 1-years survival was 80% in the CR group versus 91% in the CT group (HR = 5.50, 95%CI = 2.52-58.01, p = 0.16) and the 3-years survival was 30% versus 39% (HR = 1.50, 95% CI = 0.74-3.01, p = 0.29). Conclusion: We showed that follow-up with a chest radiography, in patients with earlier diagnosed and curative treated stage I and II NSCLC, did not give inferior clinical outcomes compared to follow-up with a CT scan. Although more investigation is needed, this study might indicate that there is no need for a CT scan as standardized follow-up.

Keywords: NSCLC stage-I, overall survival, progression free survival, oncology
Background: Clinical and pathological determinations of lymph node staging are critical in the treatment of lung cancer. However, upstaging of nodal status frequently is necessitated by postoperative findings. It is now being recognized that lung adenocarcinoma (LAC) with tumor cells arranged in a micropapillary pattern (MPP) is more malignant than those without such pattern staging. This study was conducted to evaluate clinicopathologic features that impact nodal upstaging in patients with small-sized (≤2cm) LACs with MPP (LAC-MPP). Methods: We retrospectively reviewed the 182 radically resected lung adenocarcinomas at the Kitasato University Hospital, Japan, from January 2005 to December 2015. MPP was defined as a small papillary tumor cell tuft without an obvious fibrovascular core. Tumors with ≥1% of their tumor cells arranged in a MPP were diagnosed as LAC-MPP, while the remainder were diagnosed as conventional LAC. The histological subtypes and differentiation grade of LAC were determined according to the 4th WHO classification. The registry data of the patients with LAC and LAC-MPP were analyzed, and the clinicopathologic profiles and surgical outcomes of the patients were evaluated. Results: One hundred and sixty (88%) of the total 182 were LAC whereas 22(12%) were LAC-MPP. Among the two groups, there is no significant difference in age, sex, smoking habit, preoperative serum CEA level, or surgical procedures. Compared with the LAC, the LAC-MPP had worse statuses for lymphatic invasion (p=0.0096), pleural invasion (p=0.002), postoperative lymph node metastases (p=0.001) and postoperative recurrence (p=0.002). On the other hand in clinical stages, pleural lavage cytology, and postoperative stages, there is not significant difference statistically. Median follow up time was 48 months. The five-year overall survival rates were 92% in LAC group and 85% in LAC-MPP, statistically not significant deference (p=0.98). Also with regarding to the median relapse free survival rates, no significant difference was found between two groups (p=0.14). Conclusion: The follow-up term of patients was limited and did not differ between treatment groups (p=0.14). Age was a significant determinant for MO consultation. Adjusting for sex, patients aged 41-60yrs (OR 2.38, CI:21.25-4.56) and 61-70yrs (OR 2.46, CI:31.35-4.49) were significantly more likely to have a consultation versus patients >80yrs. Other characteristics were not significantly associated with having a consultation. Conclusion: Although uptake of guideline-recommended AC is lower than expected (52%, CI:48.48-55.62), the majority of patients had an opportunity to discuss this treatment option with a MO. Patients over 80yrs were significantly less likely to have this consultation.

Keywords: lung cancer, adjuvant chemotherapy, patient decision making

P1.05-068 ELDERLY PATIENTS WITH RESECTED STAGE II NONSMALL CELL LUNG CANCER ARE LESS LIKELY TO HAVE A CONSULTATION WITH A MEDICAL ONCOLOGIST

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Background: Adjuvant chemotherapy (AC) is guideline recommended standard of care for resected Stage II NSCLC patients in Ontario. Despite evidence of a significant survival benefit, uptake of AC has been lower than expected and has remained unchanged since 2008 at 50-55%. Factors that may preclude use of chemotherapy include comorbid medical conditions, socioeconomic and demographic factors and the opportunity for consultation with a medical oncologist (MO). This study evaluated: 1) patient opportunity for a consultation with a MO, and 2) differences between patients who had a consultation and those who did not Methods: Stage II NSCLC adult patients diagnosed between 2010 and 2013 were identified using the Ontario Cancer Registry. Complete surgical resections and consultation with a MO were identified using multiple administrative databases. Receipt of guideline-recommended AC within 120 days after resection, and consultation with MO within 30 days prior and 90 days after resection were determined. Guideline-recommended AC includes platinum based regimens, including receipt outside a Regional Cancer Center (RCC). Alternative treatments were defined as non-platinum based chemotherapy or radiotherapy. Socioeconomic and demographic characteristics were compared between patients who received a consultation and those who did not. Characteristics associated with receiving a consultation were assessed using univariable analysis and multivariable logistic regression. Results: Of 778 Stage II resected NSCLC patients who survived at least 120 days, 40.9% (n=319, CI:37.40-44.42) received guideline-recommended AC, 3.0% (n=23, CI:1.70-4.40) received alternative treatment in an RCC, 11.2% (n=87, CI:8.95-13.50) received chemotherapy outside of an RCC hospital, and 45.0% (n=350, CI:41.45-48.56) of patients did not have systemic treatment after surgery. Overall, 72.9% (n=561) of patients had a consultation with a MO within 30 days prior or 90 days after resection. Of 350 patients who did not receive AC, 219 (62.6%) had a MO consultation. Median time from resection to consultation was 29 days, and did not differ between treatment groups (p=0.35). Age was a significant determinant for MO consultation. Adjusting for sex, patients aged 41-60yrs (OR 2.38, CI:21.25-4.56) and 61-70yrs (OR 2.46, CI:31.35-4.49) were significantly more likely to have a consultation versus patients >80yrs. Other characteristics were not significantly associated with having a consultation. Conclusion: Although uptake of guideline-recommended AC is lower than expected (52.1%, CI:48.48-55.62), the majority of patients had an opportunity to discuss this treatment option with a MO. Patients over 80yrs were significantly less likely to have this consultation.

Keywords: nonsmall cell lung cancer, informed decision making, adjuvant chemotherapy, elderly

P1.05-069 STAGE II NSCLC TREATED WITH NON-SURGICAL APPROACHES: A MULTI-INSTITUTION REPORT OF OUTCOMES

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Background: This study evaluated: 1) patient opportunity for a consultation with a MO, and 2) differences between patients who had a consultation and those who did not Methods: Stage II NSCLC adult patients diagnosed between 2010 and 2013 were identified using the Ontario Cancer Registry. Complete surgical resections and consultation with a MO were identified using multiple administrative databases. Receipt of guideline-recommended AC within 120 days after resection, and consultation with MO within 30 days prior and 90 days after resection were determined. Guideline-recommended AC includes platinum based regimens, including receipt outside a Regional Cancer Center (RCC). Alternative treatments were defined as non-platinum based chemotherapy or radiotherapy. Socioeconomic and demographic characteristics were compared between patients who received a consultation and those who did not. Characteristics associated with receiving a consultation were assessed using univariable analysis and multivariable logistic regression. Results: Of 778 Stage II resected NSCLC patients who survived at least 120 days, 40.9% (n=319, CI:37.40-44.42) received guideline-recommended AC, 3.0% (n=23, CI:1.70-4.40) received alternative treatment in an RCC, 11.2% (n=87, CI:8.95-13.50) received chemotherapy outside of an RCC hospital, and 45.0% (n=350, CI:41.45-48.56) of patients did not have systemic treatment after surgery. Overall, 72.9% (n=561) of patients had a consultation with a MO within 30 days prior or 90 days after resection. Of 350 patients who did not receive AC, 219 (62.6%) had a MO consultation. Median time from resection to consultation was 29 days, and did not differ between treatment groups (p=0.35). Age was a significant determinant for MO consultation. Adjusting for sex, patients aged 41-60yrs (OR 2.38, CI:21.25-4.56) and 61-70yrs (OR 2.46, CI:31.35-4.49) were significantly more likely to have a consultation versus patients >80yrs. Other characteristics were not significantly associated with having a consultation. Conclusion: Although uptake of guideline-recommended AC is lower than expected (52.1%, CI:48.48-55.62), the majority of patients had an opportunity to discuss this treatment option with a MO. Patients over 80yrs were significantly less likely to have this consultation.

Keywords: nonsmall cell lung cancer, informed decision making, adjuvant chemotherapy, elderly
Background: Standard management of stage II non-small cell lung cancer (NSCLC) is surgery, often followed by adjuvant chemotherapy. However, some patients do not undergo surgery for various reasons. The optimal non-surgical management of stage II NSCLC is undefined, with a paucity of data to guide decision making in this setting. We examined outcomes of stage II NSCLC patients who were treated with curative, non-surgical approaches. Methods: We performed a multi-institution review of stage II NSCLC patients treated non-surgically either with curative intent between January 2002 and December 2012, across three major Canadian academic cancer centres. Data on demographics, comorbidities, staging, treatment, and outcome were collected. The primary endpoint was overall survival (OS). Logistic regression and Cox proportional hazard models were used to assess for factors associated with choice of therapy and OS. Results: 158 patients were included for analysis. Median age 74 years (range 50-91), 44% female; 94% current/former smokers; 67% performance status (PS) 0-1. Stage II groupings: T2b-T3 N0 in 55%, N1 in 45%. The commonest reasons for no surgery were inadequate pulmonary reserve (27%) and medical comorbidities (24%). All patients received radical radiation therapy (RT) (median 60 Gy [range 48-75]). 73% received RT alone, 24% and 3% of patients received concurrent and sequential chemoradiotherapy (CRT), respectively. Of those who received RT only, 39% received conventional (1.82 Gy/day), 51% received hyperfractionated (2.5-4 Gy/day) and 10% received stereotactic body RT (≥7.5 Gy/day). In multivariate analyses, CRT was less likely in patients ≥70 years of age (OR 0.28, 95% CI 0.11-0.70, p = 0.006), as well as in those with higher (≥5) Charlson comorbidity scores (OR 0.34, 95% CI 0.13-0.90, p = 0.03) or low (<1000/µL) white blood cell counts (WBC) (OR 0.26, 95% CI 0.09-0.73, p = 0.01). At time of analysis, 74% were alive. Median OS was 22.9 months (95% CI 17.1-26.6 months). Patients receiving CRT had significantly longer median OS than those receiving RT alone (30 vs 18.5 months, p = 0.0019). CRT fractionation schedule (p = 0.16) and nodal status (p = 0.14) did not influence survival. After adjusting for possible confounders, treatment with CRT was associated with improved survival (HR 0.38, 95% CI 0.21-0.69, p = 0.001), while elevated WBC (HR 2.45, 95% CI 1.48-4.04, p = 0.0005) and poor PS (ECOG 3-3) (HR 1.87, 95% CI 1.16-3.63, p = 0.01) were poor prognostic factors. Conclusion: Non-surgical approaches to management of stage II NSCLC are varied. Treatment with CRT was associated with significantly longer survival compared to RT alone, and a randomized trial may be warranted in this population.

Keywords: Stage II, survival, non-small cell lung cancer, Non-surgical
sensitivity and specificity for the predictors were calculated using a receiver operating characteristic curve. The patterns of lymph node metastases were also analysed. Results: In total, 9.4% (16/171) PET-CT-diagnosed N0 NSCLC cases were pathologically N1/N2 disease. The preoperative CEA was a unique independent risk factor for lymph node metastasis (OR = 0.914, 95 CI% = 0.85–0.98, P = 0.009). According to ROC curve, we divided the patients into two groups by CEA: the (n) (n) in the CEA ≤ 6.7 and CEA ≥ 1.67 groups were 1.6% (1/64) and 16.0% (15/97), respectively (P = 0.007). In 16 patients with lymph node metastasis, 7 were N1 disease, and 6 out of 9 N2 diseases were skip N2 disease. 93.5% (15/16) lymph node metastases were found in adenocarcinoma and 11 of them were single station metastases. The metastases rates in solid and subolid lesions were 12.8% (16/125) and 0% (0/46) (P = 0.007), retrospectively. Solid/mucin/micropapillary predominant adenocarcinoma were associated with LN metastases (31.2% vs 7.1%, P = 0.01). Conclusion: The preoperative CEA was an independent risk factor for lymph node metastases in CN0 NSCLC with T ≤ 2cm. In patients with CEA ≥ 1.67, sublobar resection should be avoided before thorough lymph node sampling that include intrapulmonary lymph node while patients with CEA ≤ 1.67 may be a candidate for sublobar resection, especially in GGO lesions. In patients with solid/mucin/micropapillary predominant adenocarcinoma, sublobar resection should be avoided due to high LN metastases rate.

Keywords: non small cell lung cancer, lymph node metastases, sublobar resection, CEA

Background: Accurate clinical staging is of the utmost importance for the optimal management of patients with non-small cell lung cancer (NSCLC). The aim of this study was to identify factors associated with discordance between clinical and pathologic staging in patients with operable NSCLC. Methods: The medical records of 85 patients with early-stage NSCLC, who had been submitted to thoracotomy followed by surgical resection of the primary tumor and systematic lymph node dissection, were retrospectively reviewed. All patients were staged according to the 7th edition of the TNM staging system. The presence of postoperative upstaging or downstaging was correlated with various demographic and clinicopathological factors, including age, sex, smoking history, tumor histology, tumor size and location. Results: Discordance between clinical and surgical-pathologic staging was found in 45/85 cases (52.9%), and the majority of these patients were upstaged (35/85 cases, 41.2%). Patients with IB and IB clinical stage had the highest (77.8%) and lowest (48.1%) probability of discordance, respectively. With regard to T stage, disagreement between clinical and surgical-pathologic T stage was noted in 22/85 patients (25.9%), including 16 upstaged patients (16/85, 18.8%) and 6 downstaged patients (6/85, 7.1%). Nodal status was altered postoperatively in 39/85 cases (45.9%), including 29 upstaged patients (29/85, 34.1%) and 10 downstaged patients (10/85, 11.8%). The rate of unsuspected mediastinal lymph node involvement (pathologic stage N2) was 14.1% (12/85 patients), despite negative mediastinoscopy findings. Age was the only statistically significant factor independently associated with staging discordance (odds ratio 0.93, 95% confidence interval, 0.87 to 0.99). Conclusion: Postoperative upstaging or downstaging was observed in a relatively high percentage of our patient population, and was significantly and independently correlated with patient’s age. These observations warrant confirmation in larger prospective series of patients with early-stage NSCLC.

Keywords: non-small cell lung cancer, surgical-pathologic staging, clinical staging
was not significantly different between the two groups. Cancer-specific survival was significantly poorer in the high PLR group than in the low group (p=0.0007). Considering tumor types, patients with adenocarcinoma in the high PLR group had poorer prognosis compared to the patients with adenocarcinoma in the low PLR group (p=0.0002), but for squamous cell carcinoma and in the other tumor types, there was no significant difference (p=0.20 and p=0.86, respectively). Multivariate analysis revealed that PLR was an independent prognostic factor for the cancer-specific survival. Conclusion: In the patients who underwent anatomical resection with lung cancer, PLR was correlated with prognosis.

Keywords: PLR, NSCLC, lung cancer

P1.05-076 RISK FACTORS IN PATIENTS WITH PATHOLOGICAL STAGE I NON-SMALL CELL LUNG CANCER

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Background: Patients with pathological (p-) stage I non-small cell lung cancer (NSCLC) can have good prognosis with complete resection, whereas some patients die from disease recurrence. The aim of this study was to investigate the risk factors for p-stage I NSCLC. Methods: We retrospectively reviewed 234 patients with completely resected p-stage I NSCLC from March 2005 to December 2015. Patients with synchronous or metachronous multiple lung cancer or malignancies from other organs were excluded. Clinicopathological factors were analyzed, including age, sex, serum carcinoembryonic antigen (CEA) levels, histology, surgical procedure, tumor size, pleural invasion, lymphatic invasion, vascular invasion, and histological grade. Univariate and multivariate analyses of disease-free survival (DFS) and overall survival (OS) were performed. Results: The study group included a total 234 patients, with 119 men and 115 women, ranging in age from 22 to 88 years (mean 68±10.4 years). The median follow-up period was 50.7 months. The preoperative serum CEA level was elevated in 37 patients. Complete resection was performed in all patients, comprising pneumonectomy in one patient, and bilobectomy in two, lobectomy in 192, segmentectomy in 17, and wedge resection in 22. Adenocarcinoma, squamous cell carcinoma, and other histology were observed in 187, 38 and nine patients, respectively. The maximum tumor diameter exceeded 30 mm in 63 patients and tumor diameter was 30 mm or less in 171 patients. There were 38 patients with pleural invasion, 24 patients with lymphatic invasion, and 34 patients with vascular invasion. Multivariate analysis showed that pleural invasion and lymphatic invasion were independent factors for recurrence, whereas older age (>70 years), high serum CEA levels, pleural invasion, lymphatic invasion and vascular invasion were independent factors for poor survival. The 5-year DFS and OS in patients without pleural invasion and without lymphatic invasion were 88.5% and 93.5%, respectively, compared with 29.1% and 33.2% in patients with pleural invasion and with lymphatic invasion (p<0.001). Conclusion: Pleural invasion and lymphatic invasion were independent factors for recurrence and poor survival in p-stage I NSCLC. Adjuvant chemotherapy should be considered for patients with lymphatic invasion.

Keywords: pathological stage I, non-small cell lung cancer, risk factor

P1.05-078 THE RELATIONSHIP BETWEEN IASLC/ATS/ERS GRADING SYSTEM OF ADENOCARCINOMA OF THE LUNG AND QUANTITATIVE PET PARAMETERS

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Background: There are differences in terms of survival even in early stage adenocarcinomas and subtypes of tumor are the most particular factor. The aim of the study was to investigate the relationship between the International Association for the Study of Lung Cancer (IASLC)/American Thoracic Society (ATS)/European Respiratory Society (ERS) grading system of the adenocarcinoma and quantitative PET parameters in terms of survival. Methods: 179 operated adenocarcinoma patients categorized according to grade, histological subtypes (Table 1). All patients underwent complete resection and lymph node resection. Invasive adenocarcinoma (MIA) and adenocarcinoma in situ (AIS) were excluded. PET/CT images were re-evaluated and MTV, TLG and SUV-max of primary tumors were calculated. Correlations between quantitative PET parameters and both tumor and overall survival were analysed. Results: A strong correlation was detected in terms of tumor size between pathologic tumor size and PET-BT (r=0.01, r=0.816). If the SUV-max of tumor lymphadenopathy (LAP) ratio cut-off is taken as ≥2.5, it is significantly higher to detect metastatic lymph node (p=0.001). SUV-max value had weak negative correlation with survival (p=0.004<r<0.220). 49.6% were determined as cut-off value for MTV and 9.68 cm³ was for TLG. In the cases, while only 1.4% of all patients were treated with only surgical resection (mOS 4 months); (p=0.001). Conclusion: We analyzed the data collected at our department to assess the difference in outcomes of different strategies in IIA–N2 management. The most of our patients were treated with platinum-based doublets only, followed by sequential chemotherapy and irradiation as a second most frequent therapy option. Only 21.8% of the patients were treated with surgery only or surgery combined with other forms of treatment. Only 1 patient underwent concurrent chemoradiation. The difference in overall survival between different therapy options showed highest mOS in patients treated with neoadjuvant chemotherapy and surgery followed by sequential chemotherapy and irradiation. Sequential chemotherapy and irradiation was superior to chemotherapy. The limitation of our study was a small number of patients in this specific subgroup, as well as small number of patients who underwent concurrent chemoradiation.

Keywords: N2 disease, therapy regimens, NSCLC

P1.05-079 SURVIVAL IN PATIENTS WITH PATHOLOGICAL STAGE I NON-SMALL CELL LUNG CANCER: A SINGLE INSTITUTION EXPERIENCE

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Background: Background: There are different therapy options available for stage IIA–N2 NSCLC patients that were set by the NCCN guidelines. That is why we decided to evaluate outcome of different management strategies. Methods: Medical records of the patients diagnosed with lung cancer in Clinical hospital center Zagreb, Department for respiratory diseases Jordanovac during the year 2012 and 2013 were retrospectively collected and reviewed. Median overall survival (mOS) was measured and analyzed using the Kaplan-Meier and log-rank test. Results: There were 147 patients diagnosed with stage IIA–N2 NSCLC, out of which 105 were male (71.4%), with median age 63 (40.102). Most of them were ex-smokers (54.4%), while only 9.5% never smoked cigarettes. Most of them had very good performance status at the time of diagnosis (ECOG 0-1.91%). 78.5% of the patients were diagnosed with adenocarcinoma, 62.6%23.2% with squamous cell carcinoma, 6.4% with NSCLC-NOS and only 1.0% with adenosquamous carcinoma. mOS for all diagnosed lung cancer patients was 9 months and for NSCLC 8 months. mOS for IIAN2 NSCLC was 14 months. Our patients were treated with chemotherapy in 40.8% of the cases (mOS 11 months); sequential chemotherapy and irradiation in 25.2% (mOS 17 months); surgery, sequential chemotherapy and irradiation in 14.3% (mOS 26 months); surgery and adjuvant chemotherapy in 4.1% (mOS 15 months) and neoadjuvant chemotherapy and surgery in 1.4% (mOS 34 months) of the cases, while only 1.4% of all patients were treated with only surgical resection (mOS 4 months); (p=0.001). Conclusion: We analyzed the data collected at our department to assess the difference in outcomes of different strategies in IIA–N2 management. The most of our patients were treated with platinum-based doublets only, followed by sequential chemotherapy and irradiation as a second most frequent therapy option. Only 21.8% of the patients were treated with surgery only or surgery combined with other forms of treatment. Only 1 patient underwent concurrent chemoradiation. The difference in overall survival between different therapy options showed highest mOS in patients treated with neoadjuvant chemotherapy and surgery followed by sequential chemotherapy and irradiation. Sequential chemotherapy and irradiation was superior to chemotherapy. The limitation of our study was a small number of patients in this specific subgroup, as well as small number of patients who underwent concurrent chemoradiation.

Keywords: pathological stage I, non-small cell lung cancer, risk factor
quantitative PET parameters can help to decide on treatment options and it is possible to avoid unnecessary treatment and to decrease treatment related morbidity rate.

Keywords: Adenocarcinoma, PET-BT Parameters, New classification

POSTER SESSION 1 - P.05: EARLY STAGE NSCLC MISCHELLANEOUS
MONDAY, DECEMBER 5, 2016

P1.05-079 LUNG CANCER IN THE ELDERLY: FACTORS AFFECTING LONG-TERM SURVIVAL FOLLOWING RESECTION
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Background: Lung Cancer remains the most common cancer in the world. It has progressively become a disease of older people, with the median age at diagnosis now exceeding 65 years. As population grows older demographically, it poses various distinct treatment & management challenges. Thus, we looked into factors associated with long-term survival following pulmonary resections for lung cancer in the elderly patients 70 years or older Methods: All medical records for these elderly patients with lung cancer who ever went pulmonary resections, between years 2000 to 2010, were reviewed. These data was cross-referenced & checked with the operating theatre ORSOS & national mortality data. Results: Patients were stratified into various groups. Gender, Median age at diagnosis, patient characteristics, associated medical co-morbidities, Pre-operative lung functions tests, extent of pulmonary resections & overall 1, 2 & 5 years survival was calculated. Conclusion: Stringent & proper selection criterias in elderly patient with lung cancer undergoing pulmonary resections will identify groups of patients that will benefit from these surgeries. Thus, identifying these elderly sub-groups will give new lease of life in survivability following pulmonary resections for lung cancer.

Keywords: lung cancer, elderly, survival, NSCLC


P1.06-001 SLUGA R, ROEPMAN P, KUMMER A, VD BOSCH W, VD BORNE BEEM, SCHRAMEL FMNH
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Background: Tyrosine kinase inhibitors (TKIs) for treatment of advanced EGFR mutated adenocarcinoma were shown in many studies to be superior to chemotherapy in terms of progression-free survival. Since most data is derived from studies on Asian populations, there is a lack of data from other ethnicities. In the Netherlands the guidelines recommend that EGFR-mutation analysis should be performed in all patients with stage IIIb and IV adenocarcinoma and a non-small cell lung cancer-not otherwise specified(NSCLC-NOS). The aim of this study was to investigate the compliance to the guidelines in terms of determination of EGFR mutations, prevalence of EGFR mutations and the outcomes of treatment with the TKIs in a cohort of European patients with advanced NSCLC harboring an EGFR mutation. Methods: Data was obtained by retrospective analysis of the medical records of patients with a stage IIIb and IV non-small cell lung cancer between 2009 and 2014 in the two top-clinical hospitals in the Netherlands. Results: The total number of patients included in the study was 1022. Molecular diagnostic tests were performed in 57.3% of patients with advanced adenocarcinoma or NSCLC-NOS. The prevalence of performing molecular diagnostic tests improved significantly between 2009 and 2014 (25.2% to 74.4% respectively). Positive EGFR mutation was found in 43 patients (9.3% of all molecular diagnostic tests performed). 72.2% of patients harboring an EGFR mutation were treated with TKIs. A significant overall survival benefit with a mean survival of 763 days was seen in EGFR positive patients treated with TKIs (with or without prior/subsequent chemotherapy) versus 435 days in patients treated with conventional chemotherapy (hazard ratio (HR): 0.719. 95% confidence interval (CI): 0.587-0.881). A large fraction of the patients with EGFR-mutated tumors were either initially or after progression treated with chemotherapy. EGFR positive patients who were prior to TKI treatment treated with chemotherapy had significantly longer survival in comparison to patients treated only with chemotherapy (1201 days vs 435 days respectively (HR: 3.289, 95% CI: 1.551-6.997). 10 patients were not treated with TKIs, either because of poor performance status (40%), patient’s refusal (30%), rapid disease progression (20%) or 7970M mutation (10%). Conclusion: This study showed that incidence of molecular testing improved significantly over the course of the last years, leading to more effective targeted therapy. Overall survival was significantly prolonged in patients harboring an EGFR mutation treated with chemotherapy prior to TKIs, compared to patients without EGFR mutation treated only with conventional chemotherapy.

Keywords: NSCLC, EGFR, TKI


P1.06-002 CONTRALATERAL AXILLARY LYMPH NODE METASTASIS OF A LUNG CANCER: A CASE REPORT
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Background: Primary lung cancer metastasis to axillary lymph node is rare. Routine examination of the axilla is useful way to detect suspicious nodes. Methods: We evaluated retrospectively medical and pathological records of a male patient at our division who had a primary lung cancer with axillary lymph node metastasis. Results: A 66-year-old male presented with shortness of breath. His chest x-ray showed a large opacity in the lower one-half of the right lung field. Computed tomography (CT) imaging revealed a solid mass in the right hemithorax measuring 50x50 mm. Positron emission tomography/Computed tomography (PET/CT) demonstrated increased fluorodeoxyglucose uptake (Standard uptake value: 9.9) by the mass. Fiberoptic bronchoscopy was performed and transbronchial biopsy was consistent with squamous cell carcinoma. Mediastinoscopy was performed to evaluate the stage of the tumor and biopsies from 2R, 2L, 4R, 4L, 7L mediastinal lymph nodes had negative results. Right lower lobectomy was planned and due to invasion of the right middle lob vein and bronchus, right lower lobectomy and mediastinal lymph node dissection were performed. Pathological evaluation of the tumor and lymph nodes showed that staging of the tumor was T2b N1 (11 lymph node had metastasis, although 2,4,7,9 lymph nodes were metastasis free). Patient was discharged on post-operative 7. days and received chemotherapy 12 cycles. During follow-up PET/CT revealed increased FDG uptake by the mass in the residual right lung (SUV:3.3) and axillary subcentimetric nodule (SUV:11.3). Physical examination of the patient revealed a palpable nodule in the right axilla. Ultrasound guided needle biopsy was performed to this nodule but it had negative result. Before performing pulmonary resection, we decided to dissect this lymph node. 30 months after right lower lobectomy, axillary lymph node dissection was performed and frozen section procedure demonstrated squamous cell lung carcinoma metastasis to axillary lymph node. Pulmonary resection was cancelled and patient was discharged post-operatively 3 day and received chemotherapy again. After 6 month follow-up the patient was dead. Conclusion: Routine physical examination of axilla is recommended even if mediastinal lymph nodes metastasis are metastasis free either at initial presentation or at follow-up of patients. In this case metastatic axillary lymph node was subcentimetric, although according to Austin et al: 14 mm or larger axillary lymph nodes are suggestive of adenopathy. Fishman et al. considered 15mmor larger single axillary lymph node without fatty center as abnormal. Without mediastinal lymph nodes metastasis, contralateral axillary lymph node metastasis could be of systemic origin.

Keywords: axillary lymph node, contralateral, Advanced stage


P1.06-003 ANAMORELIN IN CACHECTIC PATIENTS WITH ADVANCED NSCLC, A POST-HOC POOLED EFFICACY DATA ANALYSIS OF TWO PHASE 3 TRIALS
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Background: Anorexia-cachexia is a multifactorial syndrome frequently experienced by patients with non-small cell lung cancer (NSCLC). It is characterized by decreased body weight (mainly due to muscle loss) and is associated with worsen morbidity, poor tolerance of chemotherapy and reduced survival. The randomized, double-blind ROMANA 1 and ROMANA 2 phase 3 trials in cachectic NSCLC patients, demonstrated that the ghrelin receptor agonist anamorelin was well tolerated, improved body weight, lean body mass (LBM), fat mass (FM) and anorexia/cachexia symptoms and concerns, with no difference in handgrip strength compared to placebo. Here we assessed pooled efficacy and numbers needed to treat (NNT) from ROMANA 1 and ROMANA 2 studies. Methods: Stage III/IV NSCLC patients with cachexia (≥5% weight loss during prior 6 months or BMI <20 kg/m²) were randomized (2:1) to daily oral 100 mg anamorelin or placebo for 12 weeks. Efficacy endpoints were changes in LBM, FM, total body mass (TB) and in self-reported anorexia/cachexia/symptoms and concerns. We present the pooled efficacy data from a post-hoc analysis from both trials (anamorelin, N=552; placebo, N=277); treatment differences, 95% CI, NNT and nominal p values from baseline to end of study. Results: At the end of study, compared with placebo, patients treated with anamorelin significantly increased body composition parameters (LBM, appendicular LBM, FM, and TB), and a greater proportion of patients showed improvements in these parameters (Table). The anamorelin group also significantly improved anorexia/cachexia symptoms and concerns, and compared to placebo, more patients in the anamorelin arm achieved the minimally important difference of 4 points.

Conclusion: Anamorelin has anabolic activity while improving symptoms and concern burden in cachectic patients with NSCLC. A significantly greater proportion of patients increased lean mass, fat mass and improved anorexia/cachexia symptoms and concern score in the anamorelin arm versus the placebo arm, with favorable NNT.

Keywords: cachexia, anamorelin, NNT, ROMANA

P1.06-004 EVALUATING THE NON-SMALL CELL LUNG CANCER SYMPTOM ASSESSMENT QUESTIONNAIRE (NSCLC-SAQ): PRELIMINARY RESULTS FROM THE QUANTITATIVE PILOT STUDY

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Background: In collaboration with the US Food and Drug Administration (FDA), the Patient-Reported Outcome (PRO) Consortium’s NSCLC Working Group has developed the 7-item NSCLC-SAQ. Content includes cough, pain (2 items), shortness of breath, fatigue (2 items), and appetite. A quantitative pilot study is underway to evaluate the NSCLC-SAQ’s item-level and scale-level performance. Methods: Eligible subjects with clinically-diagnosed advanced NSCLC from US-based clinical sites completed a questionnaire battery (demonstrations, NSCLC-SAQ, NCCN/FACT Lung Symptom Index-17 [FLSI-17], Patient Global Impression of Severity [PGIS]) using a tablet computer. For this interim analysis, items were evaluated for response distribution, ceiling/ floor effects, missing data, and item-to-item correlations. Exploratory factor and Rasch analyses were examined. Internal consistency reliability was estimated using Cronbach’s coefficient alpha. Construct validity was assessed with Pearson correlations between the NSCLC-SAQ and FLSI-17 Disease-Related Symptom (DRS) subscale. The PGIS was used to assess the NSCLC-SAQ’s known-groups validity. Results: For this interim analysis, 117 (of the anticipated 150) subjects from nine sites were included. Subjects’ mean age was 64 years old (range 40-85), 55% were female, and 84% were white (non-Hispanic), ECOG performance status at enrollment was: 0 (33%), 1(50%), and 2 (17%); NSCLC staging was: Stage IIIA (15%) and IV (85%). A total of 34% were treatment-naïve, 32% had received first-line treatment only, and 34% had received second- or third-line treatment. Mean scores for the 7 items of the NSCLC-SAQ ranged from 0.9 to 2.2 using a response scale between 0 (“No symptoms at all”) to 4 (“Very Severe Symptoms”) or “Always”). Subjects used the full range of responses (i.e., 0, 1, 2, 3, and 4) and provided answers for all NSCLC-SAQ items. Rasch analyses showed the items were ordered and the person-to-item distribution was acceptable. Factor analysis indicated a single component accounting for 47% of the variance, which supports a unidimensional scale structure and the ability to calculate a total symptom score. Cronbach’s alpha was 0.80. The NSCLC-SAQ total symptom score correlated highly (r=0.87) with the FLSI-17 DR and was able to discriminate levels of overall symptom severity as assessed by the PGIS (p<0.001). Conclusion: The NSCLC-SAQ has been developed in accordance with the FDA’s PRO Guidance. This study provides quantitative evidence of adequate item and scale performance. These data will be submitted to the FDA to support qualification of the NSCLC-SAQ as a measure to assess a symptom endpoint for efficacy evaluation and product labeling.

Keywords: symptom assessment, NSCLC-SAQ, non-small cell lung cancer
P1.06-006 TREATMENT BEYOND PROGRESSION IN PATIENTS WITH ADVANCED SQUMOUS NSCLC PARTICIPATING IN THE EXPANDED ACCESS PROGRAMME (EAP)

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Background: Response patterns of immunotherapies differ from those seen with other therapies approved for the treatment of tumors. Due to this reason, immunotherapy protocols generally allow patients (pts) to continue treatment beyond investigator-assessed radiographic progressive disease (PD) as long as there is ongoing clinical benefit, but to date no data has been reported regarding treatment beyond PD in routine clinical practice. Here we report the analysis of the subgroup of pts treated beyond initial PD in EAPs with nivolumab EAP for pts with squamous non small cell lung cancer (Sq-NSCLC). Methods: Nivolumab was available upon physician request for pts aged ≥18 years who had relapsed after a minimum of one prior systemic treatment for stage IIIIB/IV Sq-NSCLC. Nivolumab 3 mg/kg was administered intravenously every 2 weeks to a maximum of 24 months. Pts included in the analysis had received ≥1 dose of nivolumab and were monitored for adverse events (AE) using Common Terminology Criteria for Adverse Events. Patients were allowed to continue treatment beyond initial PD as long as they met the following criteria: investigator-assessed clinical benefit, absence of rapid PD, tolerance of program drug, stable performance status and no delay of an imminent intervention to prevent serious complications of PD. Results: With a median follow-up of 5.2 months (range 0.1-9.3), 363 pts were evaluable for response. Prior to first progression, the objective response rate (ORR) was 14%, with 1 complete response (CR) and 50.1% partial responses (PR), and the disease control rate (DCR) was 41%. Sixty-six pts were treated beyond RECIST defined progression, with 23 pts obtaining a non-conventional benefit, meaning a subsequent tumor reduction or stabilization in tumor lesions. In particular, 17 pts obtained a SD (95% CI: 2.3-24.6) and 6 months and 12 months OS were 75% and 53%, respectively. The safety profile was consistent to what already had not been reached (95% CI: 3.2-4.6) and 6 months and 12 months OS were 75% and 53%, respectively. The safety profile was consistent to what already had not been reached (95% CI: 3.2-4.6).

Conclusion: Patients with oligometastatic NSCLC, who continued treatment beyond PD demonstrated sustained reduction or stabilization of tumor lesions. In particular, 17 pts obtained a SD (95% CI: 2.3-24.6) and 6 months and 12 months OS were 75% and 53%, respectively. The safety profile was consistent to what already had not been reached (95% CI: 3.2-4.6) and 6 months and 12 months OS were 75% and 53%, respectively. The safety profile was consistent to what already had not been reached (95% CI: 3.2-4.6).

Keywords: oligometastatic NSCLC, Radical treatment

P1.06-007 RADICAL TREATMENT OF SYNCHRONOUS OLIGOMETASTATIC NON- SMALL CELL LUNG CANCER (NSCLC)

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Background: Cancer represents a large biological spectrum of disease ranging from localized to multisystem involvement with multiple intermediate stages. Oligometastatic NSCLC is thought to be a better opportunity for local control (OS) but there are few prospective studies that evaluate it. Methods: Prospective cohort study with NSCLC patients treated at the Instituto Nacional de Cancerología of Mexico, with stage IV and oligometastatic disease (≤5 metastatic lesions). Patients were enrolled to receive, after 4 cycles of systemic treatment with platinum-doublet chemotherapy or 4 months of tyrosine kinase inhibitors in patients with driver mutations, local consolidative treatment for the primary lesion and their metastases with chemoradiotherapy, surgery, radiotherapy, stereotactic radiosurgery or radiofrequency ablation based on the decision of the Multidisciplinary Thoracic Committee of the institute. The primary outcome was overall survival. The study was approved by the Institutional Ethics Committee and registered in clinical trials NCT02805530. Results: Up to this moment, we have evaluated 29 patients with NSCLC and oligometastatic disease. Of these, 62% were males with a median age of 58 years (IQR 52.5-64.5), median CEA 10.2 (IQR 3.2-25.5), 59% former or currently smokers (median 37.5 package/year), wood-smoke exposure 28%. Overall 90% of the patients presented adenocarcinomas, 28% EGFR mutation (50% deletion of exon 19, 38% mutation on exon 21). At diagnosis 93% of the patients had symptoms mainly cough (48%), dyspnea (30%), neurologic symptoms (26%), weight loss (28%) and dysphonia (15%). We evaluated the oligometastatic disease status with PET-CT and MRI in all the patients and the remaining with CT scan plus MRI. At diagnosis 66% had one or two metastases, 14% three to four metastases and 20% five metastases. For metastatic sites CNS was the main site of metastases in 52% of patients, 28% contralateral lung, 17% bone metastases and 7% at suprarenal. For radical treatment to the primary tumor, 59% chemoradiotherapy, 21% radiotherapy, 28% surgery and 3% radiofrequency. For definite treatment for the metastases, 45% received radiotherapy, 14% chemoradiotherapy and 17% surgery. The mean dose of radiotherapy received for the control of the primary tumor was 56.3 Gy (SD 11.22 Gy) and 29.5 Gy (SD 8.6 Gy) for metastases. After multimodal treatment 24% had radiologic complete response. The median OS were 18.26 months (95%CI:10.89-25.64), the median OS for those with and without radiologic complete response were 28.8 months (95%CI:12.98-44.14) and 14.45 months (95%CI:10.40-18.51) respectively. Conclusion: Patients with oligometastatic NSCLC with aggressive treatment have a large OS regardless their mutational status.

Keywords: oligometastatic NSCLC, Radical treatment

P1.06-008 NON-SMALL CELL LUNG CANCER IN OCTOGENARIANS: REAL-LIFE CLINICAL PRACTICE, CHARACTERISTICS, THERAPIES AND SURVIVAL

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Background: Globally, more people are surviving to older age; consequently, an increasing proportion of cancer patients are aged ≥65 years and many are aged ≥70 years. Treatment of the elderly with lung cancer has, therefore, become an important issue. We performed a retrospective study of our patients to demonstrate how octogenarians with non-small cell lung cancer (NSCLC) are treated in real-life clinical practice. Methods: A retrospective observational study of all elderly (≥80 years) patients with NSCLC referred to Department of Respiratory Medicine and Allergy, Karolinska Hospital, Sweden, 2003-2010 and followed until June, 2016. Results: During the period 2662 patients were newly diagnosed with lung cancer (≥82 (12.2%) 80 years or older. 33.6 (8.6%) had small cell lung cancer and were excluded, leaving 452 for the study. 216 (47.8%) were male. Mean, median, and range for age males were 83.8, 83, and 80-96 years, respectively. These figures for females were 83.7, 83, and 80-96. 28 (6.2%) of the population were 90 years older. 77.8% patients were current or former smokers with no significant differences between the genders (p=0.001). There was no difference in performance status (PS) between the genders (p=0.93), with PS 0 in 45%, PS 2 in 26% and PS 3-4 in 29%. 33.9% of patients were diagnosed in stages I-IV, 23.4% in stage III and 31.9% in stage IV. Most of the patients, 45.6%, had adenocarcinoma, 21.8% squamous cell carcinoma. In the study there was no difference in cancer diagnosis was unavoidable in 23.2%. There were significant differences in treatment modalities (p=0.040). Chemotherapy was given in 9.5%, local radiotherapy in 17%, stereotactic body radiotherapy (SBRT) in 10.6%, 6.9% underwent surgery and 209 (66.2%) were not given any therapy. Second-line chemotherapy was given in 46% and third-line in 3.5%. Only one patient received fourth line. Median overall survival was 115 days in patients given no therapy and 362 days in patients given any therapy. Patients who underwent surgery had a median overall survival of 5,6 years compared to 3,5 years for patients given SBRT (p=0.0187). There were no significant differences in survival between genders. Conclusion: Treatment of NSCLC patients 80 years and older with...
any modality is feasible with a good PS. Survival is fairly good with surgery or SBRT.

Keywords: Therapy, lung cancer, elderly, survival

Poster Session 1: P1.06. Advanced NSCLC & Chemotherapy/Targeted Therapy/Immunotherapy
Advanced General - Monday, December 5, 2016

P1.06-009 Determining Optimal Array Layouts for Delivering TTFIELDS to the Lungs Using Computer Simulations
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Background: Tumor Treating Fields (TTFIELDS) are low intensity, alternating electric fields in the intermediate frequency range. TTFIELDS disrupt mitosis by interfering with formation of the mitotic spindle. The therapy is FDA approved for the treatment of glioblastoma (GB). A study to assess the efficacy of TTFIELDS in combination with chemotherapy for the treatment of mesothelioma is underway, and a pivotal study testing the efficacy of TTFIELDS in NSCLC is planned. TTFIELDS are delivered through two pairs of transducer arrays applied to the patient’s skin. In-vivo and In-vitro studies suggest that treatment efficacy increases with field intensity. Therefore personalizing the array placement to deliver optimal field distributions is important and is a prerequisite when treating GB patients. However, optimal array layouts for lung cancer patients have not yet been determined. Here we present a finite element simulations-based study investigating optimal array layouts in male and female anatomic models. Methods: The study was performed using the SimLife software package and the DUKE and ELLA computational models (ZMT, Zurich, Switzerland). To represent individuals with a variety of body dimensions, the models were linearly scaled. The distribution of TTFIELDS within the thorax of these models was calculated for a set of array layouts. The layouts were ranked with highest scores for those that conformed well to body contours and delivered uniform high intensity fields to the lungs. Results: Uniform field distributions within the lungs are obtained when the arrays are axially-aligned with the parenchyma as much as anatomically possible. Generally, the layouts that received the highest scores were those in which one pair of arrays delivered an electric field from the anterolateral to the posterior-lateral aspect of the patient, with the second pair inducing the field from the antero-contralateral to the posterolateral aspect of the patient. However, due to body contours, this type of layout does not adhere well to smaller females, potentially hampering the efficient delivery of TTFIELDS. Therefore, for smaller females, a layout in which one pair of arrays is placed on the lateral and contralateral aspects of the patient, and a second set of arrays is placed on the anterior and posterior aspects of the patient is preferred. Conclusion: This study provides important insights into how TTFIELDS distribution in the lungs is influenced by the array layout. These results should be accounted for when developing guidelines for transducer array placement on the thorax.

Keywords: Novel Therapies, Tumor Treating Fields, NSCLC, TTFIELDS

P1.06-010 Analysis of the Incidence of Cancer Cachexia in Patients with Advanced Lung Cancer at Referral to a Dietitian
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Background: Lung cancer is the second most common cancer diagnosed in men and women in the UK with a very poor 5 year survival (10%). There is a lack of robust data on the stage of cachexia in which patients with lung cancer present. The occurrence of cachexia can influence overall outcomes and a patient’s quality of life. Refractory (irreversible) cachexia indicates a poor prognosis. Methods: We reviewed all patients diagnosed with metastatic primary lung cancer that were referred to the Macmillan Oncology Dietitians over a 4 year period at the Royal Surrey County Hospital. Reasons for referral commonly included: weight loss, glycaemic control in diabetes, decreased oral intake and food texture modification. We compared self-reported usual body weight (UBW) to weight at referral. Patients were defined as cachetic if weight loss was ≥5% and refractory cachexia if survival was <90 days from dietitian review. Results: 310 patients with incurable lung cancer were reviewed by the dietitian. Mean age was 68.8 (range 36-98). 42% were female, 58% were male. Mean weight loss was 10%. 76% of patients had lost ≥5% of usual body weight. Mean pre-cancer body mass index (BMI) was 26.9 (kg/m2), mean BMI at referral was 23.0 (kg/m2). Median survival of non-cachetic and cachetic cohorts were different (299 vs 188 days respectively, p=0.0078). 24% (73 patients) had refractory cachexia. Conclusion: Our study shows cachexia is very common (76%) in lung cancer and affects survival. A quarter of patients had refractory cachexia. BMI is an insensitive measure of weight loss. Early symptom control improves survival in lung cancer and this data suggests patients are routinely being referred too late to a dietitian. Cachexia in lung cancer is a significant clinical problem. Could upfront assessment of cachexia improve outcome in patients with advanced lung cancer? We propose to investigate this further.

Keywords: cachexia, metastatic, dietitian, nutrition

Poster Session 1: P1.06. Advanced NSCLC & Chemotherapy/Targeted Therapy/Immunotherapy
Advanced General - Monday, December 5, 2016

P1.06-011 Altered Body Composition and Fat Loss in Advanced Non-Small Cell Lung Cancer
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Background: Assessment of body composition, including fat mass and fat%, is a useful measure of nutritional status in cancer and may help guide nutritional interventions. However, these abnormalities have not been well documented in lung cancer. We aimed to study alterations in parameters of body composition in Non small cell lung cancer (NSCLC). Methods: A retrospective chart review was conducted of all newly diagnosed patients with NSCLC. Age and sex matched healthy controls were recruited prospectively. Disease staging was done according to the American Joint Committee on Cancer (7th edition). Performance status was assessed using the Karnofsky performance Scale(KPS), and the Eastern Cooperative Oncology Group (ECOG). Details of body composition including basal Metabolic Rate (BMR), total body water (TBW), fat mass, and Fat-free mass (FFM) were calculated by bioelectric impedance method using TANITA TBF 300 body composition analyzer. Results: A total of 256 patients (83.6% males) and 211 controls (81.5% males) were studied. The mean (SD) age of patients was 54.5 ± 9.0 years, median smoking index was 598 (range, 0-2500) and mean duration of symptoms was 158.3 (91.7) days. Median KPS was 80 (range, 40-100). Majority had Stage IV disease (54.2%), followed by Stage III (41.4%) and Stage II (4.4%). All measured components of body composition were significantly lower in NSCLC compared to controls (Table). Among patients with normal body weight (BMI 18.5 – 25 kg/m²), the TBW and FFM were significantly lower compared to their healthy counterparts.
P1.06-012 CENTRAL AND PERIPHERAL LUNG ADENOCARCINOMAS EXHIBIT DIFFERENT TIMING AND PREDILECTION FOR DISTANT METASTASIS

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Background: Although distant metastases are major factors for unfavorable prognosis in lung adenocarcinoma (ADC), metastatic patterns have not been widely analyzed in this malignancy. Methods: Clinicopathological data of 1126 ADC patients (541 men, 585 women, mean age: 62.1 ± 9.4 years, 32-88 years) were studied retrospectively, focusing on the localization of primary tumors and distant metastases. Metastases diagnosed at the time of primary tumor diagnosis were defined as early metastases. For statistical analyses, Fisher's exact test and a chi-squared independence test were performed. Results: At time of diagnosis, 621 patients had stage IV disease. 435 of them had a solitary organ metastasis, mainly in the contralateral lung (n=187), in the brain (n=66), or in the bone (n=59). During the follow-up period another 242 patients developed distant metastasis. 39% of all patients had central (i.e. endobronchially visible) tumor. In cases with early, late-, and non-metastatic disease, the proportions of central tumors were 63%, 35% and 3%, respectively. Central primary tumors were significantly more likely to give rise to early metastases than peripheral ones (p=0.021). When comparing central and peripheral lung cancers according to their metastatic sites, in central tumors lung metastases appeared significantly earlier (p=0.017), while in peripheral ones bone metastases appeared significantly later (p=0.015). There were significant differences in the metastatic organ distributions of central vs. peripheral primary tumors for early (p=0.025) and late (p=0.009) metastases. There was no significant difference in the metastatic organ distributions of right vs. left lung primaries both for early and late metastases. In right lung tumors brain metastases appeared later (p=0.047). No significant difference was observed in the metastatic organ distributions of primary tumors of the upper vs. lower lobes for early (p=0.051), and late (p=0.528) metastases. Early appearance was characteristic for lung, pleural, and adrenal involvement (p=0.001 in all comparisons), while late development was typical for brain metastasis (p=0.002). Bone, liver, subcutaneous, and pericardial metastases showed no such tendencies. Conclusion: There are significant differences in metastatic organ distributions of central vs. peripheral lung cancers both for early and late metastases. Central primary tumors are more likely to give rise to early metastases than peripheral ones. Results of molecular subgroup analyses will be presented during the Conference.

Keywords: lung adenocarcinoma, primary tumor localization, distant metastasis, early metastasis

P1.06-013 PATIENT CHARACTERISTICS AND SURVIVAL: A REAL-WORLD ANALYSIS OF US VETERANS WITH STAGE IV ADENOCARCINOMA VS SQUAMOUS NSCLC

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Background: 5-year survival rate in patients with stage IV NSCLC was 1%. Stage IV adenocarcinoma (ADENO) and squamous (SCC) account for 44% and 18% of stage IV NSCLC diagnoses, respectively. Comparatively few characteristics and survival in US veterans with stage IV ADENO vs SCC were examined. Methods: Patients with a unique diagnosis of stage IV NSCLC between 1/1/2010 and 12/31/2015 from the US Veterans Affairs (VA) health system database were included. Lung cancer diagnoses were confirmed by VA Central Cancer Registry and Veterans Health Administration National Patient Care Database. Patients were excluded if they did not have a VA visit within 1 year before diagnosis. Results: 13,956 patients with stage IV NSCLC were included (ADENO: n=6525 [47%]; SCC: n=3421 [25%]). Baseline characteristics were similar for ADENO vs SCC, including age at diagnosis (mean, 68.8 vs 69.2 y), married at diagnosis (43.9% vs 42.2%), had known Agent Orange exposure (17.4% vs 16.3%), and the majority were white (60.8% vs 63.8%). For ADENO vs SCC, more patients were former smokers (39.5% vs 34.3%), but fewer were current smokers (53.9% vs 61.1%). For ADENO vs SCC, occurrence of brain or bone metastases were higher and incidence of chronic obstructive pulmonary disease (COPD) chronic pulmonary disease were lower (Table); age at death (mean, 69.3 vs 69.7 y) and time from diagnosis to death (TDD; mean, 0.56 vs 0.55 y) were similar. More ADENO vs SCC patients received chemotheraphy (48.5% vs 44.1%). Mean TDD was longer in patients treated with chemotherapy vs not (ADENO: 0.86 vs 0.31 y; SCC: 0.84 vs 0.35).

Conclusion: ADENO was more prevalent than SCC in veterans with stage IV NSCLC, similar to the overall population; stage IV SCC prevalence was higher in the veterans than in the overall population. Mean TDD was longer in chemotherapy-treated patients regardless of histology.

Keywords: stage IV, Real-World Analysis, Veterans, NSCLC

P1.06-014 WHAT FACTORS DETERMINE TREATMENT SATISFACTION IN PATIENTS WITH ADVANCED NSCLC RECEIVING CHEMOTHERAPY?

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Background: 5-year survival rate in patients with stage IV NSCLC was 1%. Stage IV adenocarcinoma (ADENO) and squamous (SCC) account for 44% and 18% of stage IV NSCLC diagnoses, respectively. Comparatively few characteristics and survival in US veterans with stage IV ADENO vs SCC were examined. Methods: Patients with a unique diagnosis of stage IV NSCLC between 1/1/2010 and 12/31/2015 from the US Veterans Affairs (VA) health system database were included. Lung cancer diagnoses were confirmed by VA Central Cancer Registry and Veterans Health Administration National Patient Care Database. Patients were excluded if they did not have a VA visit within 1 year before diagnosis. Results: 13,956 patients with stage IV NSCLC were included (ADENO: n=6525 [47%]; SCC: n=3421 [25%]). Baseline characteristics were similar for ADENO vs SCC, including age at diagnosis (mean, 68.8 vs 69.2 y), married at diagnosis (43.9% vs 42.2%), had known Agent Orange exposure (17.4% vs 16.3%), and the majority were white (60.8% vs 63.8%). For ADENO vs SCC, more patients were former smokers (39.5% vs 34.3%), but fewer were current smokers (53.9% vs 61.1%). For ADENO vs SCC, occurrence of brain or bone metastases were higher and incidence of chronic obstructive pulmonary disease (COPD) chronic pulmonary disease were lower (Table); age at death (mean, 69.3 vs 69.7 y) and time from diagnosis to death (TDD; mean, 0.56 vs 0.55 y) were similar. More ADENO vs SCC patients received chemotheraphy (48.5% vs 44.1%). Mean TDD was longer in patients treated with chemotherapy vs not (ADENO: 0.86 vs 0.31 y; SCC: 0.84 vs 0.35).

Conclusion: ADENO was more prevalent than SCC in veterans with stage IV NSCLC, similar to the overall population; stage IV SCC prevalence was higher in the veterans than in the overall population. Mean TDD was longer in chemotherapy-treated patients regardless of histology.

Keywords: stage IV, Real-World Analysis, Veterans, NSCLC

Abstracts
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Background: In advanced non-small cell lung cancer (NSCLC) treatment decisions regarding palliative chemotherapy are complex due to limited survival gain and treatment-related toxicities. Insight into determinants of patients' treatment satisfaction may impact decision-making and patient care. We determined the relation of patient- and treatment-related variables to treatment satisfaction. Methods: In a prospective observational multi-center study, patients with stage IIIB or IV NSCLC receiving pemtrexed (PEM)-based chemotherapy as first- or second-line treatment were enrolled. After four cycles of chemotherapy, patients completed the WHO Quality of Life-BREF (WHOQOL-BREF), which contains one item measuring overall QoL on a 1-5 scale, and the Cancer Therapy Satisfaction Questionnaire (CTSQ). The CTSQ was recently validated (Cheung et al, Qual Life Res. 2016;25(1):71-80). It consists of 16 items scored on a 1-5 scale and contains three domains. Only satisfaction with therapy (SWT) and feelings about side effects (FSE) were used. The domain scores range between 0-100, with higher scores representing better SWT and more positive FSE. We collected sociodemographic information and ECOG performance status at baseline. Adverse events (cancer- or therapy-related) during treatment were weekly registered (CTCAE 3.0). Tumor response measurements were obtained (RECIST 1.1). Patient- and treatment-related determinants univariably associated with SWT (p<0.05) were analyzed using multivariable linear regression (method: Enter). Results: Of the 95 patients receiving four cycles of chemotherapy, 69 patients completed the CTSQ. The majority of these patients had stage IV NSCLC (87.7%) and received PEM-based therapy as first-line treatment (92.3%). Treatment resulted in stable disease (SD; 53.8%), partial response (PR; 20.8%), and complete response (CR; 3.2%). However, in patients with better FSE treatment satisfaction was higher. Therefore, patients' education about and management of adverse events may have added value in maintaining patients' well-being during chemotherapy, ultimately resulting in higher treatment satisfaction. This study is funded by ZonMw, the Netherlands.

Keywords: advanced NSCLC, treatment satisfaction, chemotherapy, pemtrexed element simulations using realistic computational phantoms were used to evaluate the field distribution generated by these arrays, and optimize their design. Results: Novel array designs for delivering TTFields to the lungs were developed. These arrays are not designed as large patches, but comprise sets of interconnected small patches that adhere to the natural contours of the patient's body. Simulations showed that these arrays deliver uniform field distributions to the lungs. A particularly noteworthy design is a pair of arrays in which one array was shaped as a circular ring placed around the neck and shoulders, and the second array was shaped as a belt placed on the lower torso. This design yielded a highly uniform and intense field directed longitudinally throughout the torso. Conclusion: The arrays presented in this study deliver high field intensities to the thorax whilst maintaining patient comfort. These designs could help to improve the outcome of TTFields therapy.

Keywords: Novel Therapy, TTFields, Tumor Treating Fields

POSTER SESSION 1: P1.06: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/ IMMUNOTHERAPY
ADVANCED GENERAL - MONDAY, DECEMBER 5, 2016

P1.06-015 DESIGNING TRANSDUCER ARRAYS FOR THE DELIVERY OF TTFIELDS WHILST MAXIMIZING PATIENT COMFORT AND FIELD INTENSITY IN THE THORAX
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Background: Tumor Treating Fields (TTFields) are an anti-mitotic therapy that utilizes low intensity electric fields in the intermediate frequency range to disrupt cell division. A study to test the efficacy of TTFields in combination with chemotherapy for the treatment of mesothelioma is underway, and a pivotal study testing the efficacy of TTFields in treating NSCLC is planned. TTFields are delivered via two pairs of transducer arrays placed on the patient’s skin. The arrays comprise a set of ceramic disks that make electric contact with the skin through a thin layer of conductive medical gel. The disks in the arrays currently in use are arranged in an almost rectangular pattern. One pair of arrays is placed on the posterior and anterior sides of the patient’s thorax. The other pair is placed on the lateral and contralateral aspects of the patient. This configuration has several limitations: The array placed on the chest may not adhere well to body curvature, leading to sub-optimal electric contact that reduces field intensity in the tumor. In females and obese individuals, fields generated by arrays placed on the anterior and posterior have to traverse thick layers of adipose in the breast. The high resistivity of these layers damps the intensity of TTFields in the lungs.

Here we present novel array designs intended to overcome these limitations. Methods: Multiple concepts for arrays designed to adhere comfortably to the body, whilst avoiding regions of high adipose were proposed. Finite

POSTER SESSION 1: P1.06: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/ IMMUNOTHERAPY
ADVANCED GENERAL - MONDAY, DECEMBER 5, 2016

P1.06-016 PULMONARY TUBERCULOSIS AMONG NEWLY DIAGNOSED-THERAPY NAIVE ADVANCED NSCLC IN PERSAHABATAN HOSPITAL JAKARTA INDONESIA
Jamal Zaini1, Sita Laksmi Andarini2, Ririen R Ramadhani2, Elsia Syahrudin2, Achmad Hudoyo2
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Background: The prevalence of lung cancer increased in the recent years in Indonesia, meanwhile pulmonary tuberculosis (TB) is still a major public health problems in this community. Malignancy such as lung cancer increase the risk of tuberculosis infection and reactivation, therefore evaluation of tuberculosis among lung cancer patients is needed Methods: Newly diagnosed, therapy-naive advanced NSCLC subjects were enrolled from a referral respiratory hospital Persahabatan Hospital Jakarta Indonesia between 2014-2015. Active pulmonary tuberculosis were diagnosed by Xpert MTB/RIF from induced sputum and LPA M. TB culture. Latent Tuberculosis Infection (LTBI) was determined by Quantiferon-TB Gold-In-Tube (QFT-GIT). Demographic and clinical characteristics were evaluated. Results: Of 50 lung cancer subjects enrolled, 30 (60%) men with mean of age 55 years old (31-74 years old). Eighty five percent were adenocarcinoma (42 subjects) and 15% squamous cell lung cancer. Most of them were at end stage (87% stage IV and 13%stage IIIB) with WHO performance status (PS) 1 to 3 (20% PS 1, 70% PS 2 and 10% PS 3). Comorbidities among this group were COPD (3 subjects), diabetes mellitus (2 subjects), hypertension (6 subjects), congestive heart failure (1 subject). Active tuberculosis were diagnosed in 2% (1 subject). Based on Quantifieron results, 14% were positive (7 subjects) and classified as latent tuberculosis infection (LTBI); 50 (30 subjects) classified as non-LTBI (negative Quantiferon result) but 12 (24%) indeterminate cases. The characteristics of LTBI patients were 67% men, two third were adenocarcinomas, 80% stage IV of lung cancer, 80% having WHO PS 2 and 3, 50% were underweight (body mass index (BMI) < 17.5. Conclusion: Active pulmonary tuberculosis and latent tuberculosis infection is common among newly diagnosed therapy naive advanced NSCLC in this population. Most of them are men, adenocarcinoma, PS 2-3, and half of them were underweight.

Keywords: advanced NSCLC, active tuberculosis, LTBI

POSTER SESSION 1: P1.06: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/ IMMUNOTHERAPY
ADVANCED GENERAL - MONDAY, DECEMBER 5, 2016

P1.06-017 OBSERVATIONAL STUDY ON PROLONGED DISEASE STABILIZATION IN ADVANCED NSCLC EGFRTM WT/UNKNOWN PATIENTS TREATED WITH ERLOTI尼BIN IN SECOND LINE
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Background: In advanced NSCLC, erlotinib treatment was shown to improve survival independently of EGFR status and induce high rates of prolonged stable disease (SD). It has previously been reported that, after second-third line erlotinib, PFS and OS are long-lasting and similar between patients with SD ≥8 months and those attaining partial/complete response (PR/CR). The present study investigates the clinical value of SD in a real-world setting of advanced NSCLC. Methods: This Italian multicenter observational study enrolled patients with stage IIIb-IV NSCLC on second-line erlotinib and wild-type/unknown EGFR mutational status, with SD, CR or PR per RECIST v1.1 lasting for ≥4 weeks. Patients were observed from the beginning of erlotinib for approximately 8 months or until death. Primary end-points were the rate and duration of SD (i.e. time interval from erlotinib start to the last evidence of SD by RECIST) or CR/PR. Secondary end-points were OS and PFS (i.e. time interval from the erlotinib start to the first evidence of progression), estimated by the Kaplan-Meier method and calculated by response duration or disease stabilization. Adverse events occurring during the observation period were also recorded. Results: At the cut-off date of 30/04/16, 144/172 (83.7%) enrolled patients were evaluable for response (mean age 69.1 years, 61.8% males). At the start of erlotinib treatment, 85.4% were non-smokers, 89.6% had an EGFR-PS of 0-1, and 84.7% had stage IV NSCLC (83.3% adenocarcinoma and 11.8% squamous cell carcinoma). Following second-line erlotinib, 82.6% (119/144) of patients achieved SD and 17.4% (25/144) PR. Notably, SD was maintained for ≥8 months in 27% (39/144) of cases. At the end of the observation period, 12 (8.3%) patients had deceased, none with SD ≥8 months. Median OS had not been reached by the entire population. According to SD duration, median OS was 4.3 months if <2 months, 6.8 if between 2 and 5 months, and not reached if ≥5 months or if PR. Median PFS was 9.0 months in the entire population, 8.7 among patients with SD and 10.8 with PR. According to SD duration, PFS was 1.4 if <2 months, 4.4 months if between 2 and 5 months, 7.5 if between 5 and 8 months and 10.5 if ≥8 months. No unexpected toxicities were observed. Conclusion: In advanced NSCLC, second-line erlotinib yielded a high rate of SD; lasting ≥8 months in 27% of cases, with PFS similar to PR patients and low mortality rate.

Keywords: Erlotinib, EGFR wild-type, stable disease, advanced NSCLC

P1.06-018 TREATMENT PATTERNS AND CLINICAL PRACTICES OF ADVANCED (STAGE IV) NON-SMALL CELL LUNG CANCER (NSCLC) IN EUROPE - A STRUCTURED LITERATURE REVIEW

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Background: Non-small cell lung cancer (NSCLC) is associated with high mortality and a poor five-year survival. Novel therapies in the pipeline hold the promise to address these unmet needs and improve prognosis. Furthermore, their introduction is expected to bring considerable changes to the European treatment landscape. The aim of this review is to provide an overview of the current treatment patterns for advanced (stage IV) NSCLC in five European countries (EUS, France, Germany, Italy, Spain and the UK). Methods: A structured literature search was conducted in electronic databases for studies published between January 2010 and February 2016 to identify publications reporting on treatments for stage IV NSCLC in European populations. Additional literature searches of relevant European conferences and internet-based sources were performed to ensure the most up-to-date evidence and published clinical guidelines in the EUS countries were captured. Results: A total of nine relevant articles (five full-text studies and four conference abstracts) as well as ten clinical guidelines were eligible for inclusion in the literature review. Adverse event profiles were observed. Studies of advanced NSCLC treatment patterns in the EUS with data collected between 2005 and 2014. The most commonly reported first-line treatments were cisplatin, carboplatin and pemetrexed, a trend supported by data from individual countries where platinum-based regimens were the most widely prescribed. Other systemic treatments received included non-platinum based regimens, bevacizumab and investigational drugs. The most common second- and third-line treatment options were docetaxel, erlotinib and gemcitabine. There was limited published literature on lines of treatment prescribed in the UK whereby only information on second-line prescribed therapies was available. These included docetaxel, erlotinib, and pemetrexed. Based on this data, treatment patterns appear to be in-line with recommendations from European and national guidelines of NSCLC treatments with the exception of crizotinib and afatinib, which were not approved at the time of the data collection for the majority of studies included in the literature review. Conclusion: Treatment practices in advanced NSCLC are similar across EUS countries with slight variations depending on the time period assessed and most notably on the approval and availability of novel therapies. Overall, treatments reported as part of clinical practices across EUS countries prior to 2010 are still recommended by both national and European guidelines. Furthermore, there is a paucity of comprehensive treatment patterns information for the UK.

Keywords: treatment patterns, clinical practice, NSCLC, systematic literature review

P1.06-020 PREVALENCE OF AUTOIMMUNE DISEASE IN US VETERANS WITH NON-SMALL CELL LUNG CANCER (NSCLC)

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Background: In stage IV non-small cell lung cancer (NSCLC) patients with multiple metastases, a various pattern of disease progression is observed, including the growth of only primary site, the growth of only pre-existing metastatic site, or the growth of both metastatic sites. The aim of the study is to evaluate the detailed recurrence pattern in patients with stage IV NSCLC, and is also to evaluate whether a specific patient’s population exists whose disease progression is well controlled by the additional local therapy, such as surgery or radiotherapy to the primary or pre-existing metastatic site, during or after the systemic chemotherapy. Methods: NSCLC patients in stage IV admitted to our hospital from 2012 to 2014 were examined retrospectively. The recurrence pattern was classified in to the following groups; the growth of primary site, the growth of pre-existing metastatic site, or the appearance of new metastatic site. Furthermore, progression-free survival (PFS), overall survival (OS), and new lesion-free survival (NFS) of these groups were examined, respectively. Results: Patients treated with chemotherapy for stage IV NSCLC were 174 cases. The median age was 70 years old, and male was 74 cases. The number of platinum-based combination regimen was 71 cases, monotherapy was 66 cases, epidermal growth factor receptor tyrosine kinase inhibitor was 25 cases, crizotinib was 2 cases. In the first-line chemotherapy, median PFS, median OS and median NFS in all patients were 172 days, 417 days and 270 days. Median PFS, median OS and median NFS in patients for the growth of pre-existing metastatic site were 171 days, 250 days and 205 days. Median PFS, median OS and median NFS in patients for the growth of primary site were 235 days, not reached and not reached. Median PFS, median OS and median NFS in patients for the growth of pre-existing metastatic site were 149 days, 423 days and 149 days. Conclusion: The prognosis of the appearance of new metastatic site group seems to be worse than the growth of primary site group in the pattern of disease progression in the first-line new metastatic site. The prognosis of the growth of pre-existing metastatic site group seems to be worse than the appearance of new metastatic site group. In the stage IV NSCLC therapy, there is a possibility that the treatment outcomes will be improved according to well controlled the pre-existing metastatic site by the additional local therapy.

Keywords: local therapy, systemic chemotherapy, NSCLC

S349
Background: Immuno-therapy has emerged as an effective treatment strategy in cancer; patients with preexisting autoimmune diseases are often restricted from use. The prevalence of autoimmune disease was 12.5% worldwide (Lerner, Int J of Cellic Disease, 2015) and 24.6% in US patients with lung cancer (LC) (Khan, JAMA Oncol 2016). We report autoimmune disease prevalence in veterans with NSCLC in a real-world setting. Methods: Patients with a unique diagnosis of NSCLC between 1/1/2010 and 12/31/2015 were included. Diagnoses were confirmed by VA Central Cancer Registry and Veterans Health Administration National Patient Care Database. Patients were excluded if they had a VA visit within 1 year prior to diagnosis. Baseline autoimmune diseases were identified using ICD-9 codes for 36 organ-specific and 7 systemic autoimmune diseases. Autoimmune disease was defined as having ≥1 claim of any type (Broad definition) or having ≥1 inpatient claim or ≥2 outpatient claims ≥30 days apart (narrow definition). Results: With 341,371 patients with NSCLC were included (stage IV adenocarcinoma n=6525, stage IV squamous cell carcinoma (SCC) n=3421). Almost all patients were male (99.9%). Autoimmune disease prevalence was greater by broad vs narrow definition in all patients (15.7% vs 10.0%), adenocarcinoma patients (15.4% vs 11.0%), and SCC patients (10.5% vs 12.3%). By broad definition, 13.4% of all patients, 11.7% of patients with stage IV adenocarcinoma, and 13.0% of patients with stage IV SCC had ≥1 autoimmune disease; 2.3%, 1.7% and 2.0% had ≥1 autoimmune disease, respectively. The most common autoimmune diseases in all 3 patient populations were psoriasis, chronic rheumatic heart disease (CRHD), rheumatoid arthritis (RA), Addison disease, and ulcerative colitis (Table). Keywords: NSCLC, real-world setting, Autoimmune, Veterans

### Table: Autoimmune Disease Prevalence

<table>
<thead>
<tr>
<th>Disease</th>
<th>NSCLC n (%)</th>
<th>Stage IV Adenocarcinoma n (%)</th>
<th>Stage IV Squamous n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psoriasis</td>
<td>1507 (3.7%)</td>
<td>197 (3.0%)</td>
<td>120 (0.5%)</td>
</tr>
<tr>
<td>Broad</td>
<td>1449 (3.6%)</td>
<td>182 (2.8%)</td>
<td>116 (0.3%)</td>
</tr>
<tr>
<td>Narrow</td>
<td>1494 (3.7%)</td>
<td>182 (2.9%)</td>
<td>120 (0.5%)</td>
</tr>
<tr>
<td>CRHD</td>
<td>181 (0.4%)</td>
<td>26 (0.3%)</td>
<td>26 (0.3%)</td>
</tr>
<tr>
<td>Broad</td>
<td>1111 (2.6%)</td>
<td>182 (2.6%)</td>
<td>160 (0.4%)</td>
</tr>
<tr>
<td>Narrow</td>
<td>1133 (2.7%)</td>
<td>178 (2.7%)</td>
<td>116 (0.4%)</td>
</tr>
<tr>
<td>RA</td>
<td>1244 (3.4%)</td>
<td>162 (2.5%)</td>
<td>103 (0.3%)</td>
</tr>
<tr>
<td>Addison disease</td>
<td>352 (0.9%)</td>
<td>62 (1.0%)</td>
<td>35 (0.1%)</td>
</tr>
<tr>
<td>Broad</td>
<td>108 (0.3%)</td>
<td>13 (0.2%)</td>
<td>9 (0.0%)</td>
</tr>
<tr>
<td>Narrow</td>
<td>346 (0.9%)</td>
<td>44 (0.7%)</td>
<td>33 (0.7%)</td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td>100 (0.1%)</td>
<td>13 (0.2%)</td>
<td>9 (0.0%)</td>
</tr>
</tbody>
</table>

Conclusion: Prevalence of autoimmune disease was lower in the predominantly male US veterans with NSCLC than the general population with LC, the prevalence was similar regardless of stage or histology. The most frequent autoimmune diseases were psoriasis, CRHD, and RA.

Keywords: NSCLC, real-world setting, Autoimmune, Veterans

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### Poster Session 1: P1.06-022 Clinical Characteristics of Survival Outliers in Stage IV Adenocarcinoma Lung Cancer Patients

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Background: Lung cancer is the leading cause of cancer deaths among men and women in Canada. Many lung cancer patients are diagnosed at advanced stages of disease, which is associated with poor survival outcomes. The mean survival of stage IV non-small cell lung cancer (NSCLC) patients is typically less than 12 months; however, there appears to be a small subset of patients with advanced disease that live substantially longer than the norm. Our study aims to determine whether certain clinical characteristics correlate with longer survival in stage IV NSCLC patients. Methods: Data on 1803 stage IV NSCLC patients (1291 adenocarcinoma, 512 squamous cell carcinoma) from 1999-2011 were extracted from the Glans Look Lung Cancer database. Adenocarcinoma data is presented here; squamous cell carcinoma data analysis is ongoing. Clinical characteristics such as age, gender, ethnicity, smoking history, histology, molecular testing, metastatic disease, treatments, and socioeconomic factors were compared between survival outliers and patients with average survival. Survival outliers were defined as those patients who lived > 5 years, or greater than 2 standard deviations from mean survival (42.1 months). Results: In the survival outlier group, there were 62-25 patients who lived >5 years, and 59 who lived >42.1 months. Survival outliers included a higher percentage of females, had a smaller smoking history, smaller tumour size at diagnosis, received more treatment lines, and had fewer metastatic disease burden at diagnosis (P<0.05 in the outlier group with survival >42.1 months). Upon further characterization of metastatic disease, there appears to be survival outliers associated with no liver metastases and less sites of metastases at diagnosis, as well as with stage M1a disease compared to stage M1b. Conclusion: Adenocarcinoma patients with localized and lower metastatic disease burden and no liver metastases at the time of diagnosis appeared to live longer than their counterparts. Further statistical analysis is ongoing to determine the significance of other clinical characteristics with respect to survival. The present study will help us better understand the importance of various clinical parameters and their association with survival, in hopes of improving outcomes for lung cancer patients in the future.

Keywords: stage IV adenocarcinoma, Survival Outliers

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### Poster Session 1: P1.06-023 Clinicopathological Characteristics of Therapy (3L+T). 85% (n=110) of the NSq and 40% (n=17) of the squamous (Sq) patients received at least one Bmx test. 81% (n=105) and 19% (n=25) of NSq patients, and 40% (n=17) and 24% (n=4) of Sq patients received an EGFR and ALK test, respectively. EGFR Tyrokinase Inhibitors were most commonly used among NSq EGFR mutated patients (n=44) across all lines. 86% (n=38) of the patients received Gefitinib in 1LT and Erlotinib was used in 2LT (n=11 of 30, 37%) and 3LT (n=9 of 15, 60%) patients. All ALK positive patients (n=2) in 1L received anti-ALK therapy (Crizotinib). Among NSq EGFR/ALK negative or unknown patients receiving 2LT (n=43) and 3LT (n=22), most commonly docetaxel (n=15, 35% & n=5, 23%). Majority of the I LT patients with Sq histology (36/43, 84%) received platinum combinations therapy, most commonly carboplatin+paclitaxel (51%). Among 2LT, 67% (n=20) received a single agent, most commonly docetaxel (n=14, 47%). Single agents were commonly used in 73% (n=11) of the patients receiving 3LT. Overall, the average length of stay, regardless of line of therapy, was 24.6 days per admission. Duration of treatment was longest for 1LT (mean 129 (117 to 176) days), followed by 2LT (66 (129) days) and 3LT (65 (83) days). Median OS for Japan from start of 1LT & 2LT was 9.9 and 4.7 months, respectively. Conclusion: NSq patients are frequently tested for Bmx in Japan. Treatment is personalized according to mutation status and is in concordance with recommended guidelines.

Keywords: lung cancer, treatment patterns, HEALTHCARE RESOURCE USE, JAPAN
AXILLARY LYMPH NODE METASTASIS IN LUNG CANCER

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Background: The morbidity and mortality of lung cancer are rather high. One major metastasis pathway of lung cancer is lymph node metastasis. The incidence of axillary lymph node metastasis (ALNM) is rare, and little is known about its clinicopathological characteristics. Methods: The clinical data of 91 patients with ALNM who were treated in Zhejiang Cancer Hospital from January 1, 2007 to December 31, 2013 were retrospectively analyzed. The relevance of tumor site, local lymph node site and axillary lymph node site were checked by contingency table. Survival rates were calculated by the Kaplan-Meier method and compared by the log-rank test. Results: Lung cancer patients with ALNM were often presented with adenocarcinoma (59.3%), peripheral tumor type (71.4%), pleural invasion with pleural effusion (48.4%) or chest wall invasion (52.7%). There was a relationship between tumor site (P<0.001), local lymph node site (P<0.001) and axillary lymph node site. The median survival time of lung cancer patients with ALNM was 19.02 months, 2-year survival rate is 62.64%. Patients detected with ALNM at the initial diagnosis had poorer prognosis (P=0.002).

Conclusion: ALNM from lung cancer is rare, it may be involved through direct chest wall invasion, spread from supraclavicular and mediastinal lymph node metastasis or systemic origin. Patients detected with ALNM at the initial diagnosis had poorer prognosis.

Keywords: axillary lymph node metastasis, lung cancer, clinicopathological characteristics, Prognosis

AXILLARY LYMPH NODE METASTASIS IN LUNG CANCER

Yue Kong, Ming Chen
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Background: The morbidity and mortality of lung cancer are rather high. One major metastasis pathway of lung cancer is lymph node metastasis. The incidence of axillary lymph node metastasis (ALNM) is rare, and little is known about its clinicopathological characteristics. Methods: The clinical data of 91 patients with ALNM who were treated in Zhejiang Cancer Hospital from January 1, 2007 to December 31, 2013 were retrospectively analyzed. The relevance of tumor site, local lymph node site and axillary lymph node site were checked by contingency table. Survival rates were calculated by the Kaplan-Meier method and compared by the log-rank test. Results: Lung cancer patients with ALNM were often presented with adenocarcinoma (59.3%), peripheral tumor type (71.4%), pleural invasion with pleural effusion (48.4%) or chest wall invasion (52.7%). There was a relationship between tumor site (P<0.001), local lymph node site (P<0.001) and axillary lymph node site. The median survival time of lung cancer patients with ALNM was 19.02 months, 2-year survival rate is 62.64%. Patients detected with ALNM at the initial diagnosis had poorer prognosis (P=0.002).

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POSTER SESSION 1: P.06: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/ IMMUNOTHERAPY
ADVANCED GENERAL
MONDAY, DECEMBER 5, 2016

P1.06-025 ANALYSIS OF RISK FACTORS FOR DEVELOPMENT OF SKELETAL-RELATED EVENTS IN WOMEN WITH BONE METASTASES FROM NSCLC AND BREAST CANCER

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Background: Bone metastasis (BM) are common (up to 50%) in patients with advanced non-small cell lung cancer (NSCLC) and other malignancies, including prostate cancer and breast cancer (BC). In patients with BMs, the onset of skeletal-related events (SREs), such as pathological fracture, malignant hypercalcemia, or spinal cord compression requiring surgery or radiation therapy, seriously affects the quality of life of patients and overall survival. The purpose of this study was to analyze the risk factors (RFs) for development of SREs in women with advanced NSCLC and BC, with the aim of highlighting the differences (if any) between the two groups of patients. Methods: The medical records of 16 women with BMs from NSCLC (Group A) and 15 women with BMs from luminal-type BC (Group B) were reviewed. The following RFs have been considered: age >65 years, ECOG performance status (PS) ≥2, the presence of extra-skeletal metastases (ESM) or hypercalcemia (≥2.65 mmol/L), and number of BMs >1. Odds ratio (OR) estimates and the relative 95% confidence interval (CI) were calculated. A p-value level <0.05 was considered statistically significant. Results: During follow-up, 5 (33.3%) Group A and 11 (66.6%) Group B patients developed SREs (OR=4.40, P=0.04, respectively. The results are reported in the Table. No significant difference (p=NS) was found between groups in relation to ECOG-PS, ESM or hypercalcemia, and number of BMs. Only the age >65 years (OR=2.20, P=0.04) represented a weak significant risk factor.

Parameter | NSCLC | BC | OR | 95% CI | p-value
---|---|---|---|---|---
No. of patients | 15 | 16 | - | - | -
Skeletal-related events | 33.3% | 68.7% | 4.40 | 0.97-19.85 | 0.04
Age >65 years | 73.3% | 37.5% | 0.22 | 0.05-1.01 | 0.04
ECOG-Performance status ≥2 | 40.0% | 18.8% | 0.34 | 0.07-1.76 | 0.25
Extra-skeletal metastases | 26.7% | 43.7% | 2.14 | 0.47-9.70 | 0.32
Malignant hypercalcemia | 26.7% | 12.5% | 0.39 | 0.06-2.55 | 0.39
Multiple bone metastases | 53.3% | 37.5% | 0.52 | 0.12-2.20 | 0.38

POSTER SESSION 1: P.06: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/ IMMUNOTHERAPY
ADVANCED GENERAL
MONDAY, DECEMBER 5, 2016

P1.06-024 DISTINCTIVE PATTERNS OF PRIMARY METASTASES AND CLINICAL OUTCOMES ACCORDING TO THE HISTOLOGICAL SUBTYPES IN STAGE IV NON-CELL LUNG CANCER

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Background: The purpose of this study was to compare the primary patterns of metastases and clinical outcomes between adenocarcinoma (Adenoca) and squamous cell carcinoma (SQ) in initially diagnosed stage IV non-small cell lung cancer (NSCLC). Methods: Between June 2007 and June 2013, a total of 427 eligible patients were analyzed. These patients were histologically confirmed as Adenoca or SQ and underwent systemic imaging studies, including 18F-fluorodeoxyglucose positron emission tomography/ computed tomography and brain imaging. Synchronous metastatic sites were categorized into 7 areas, and whole-body metastatic scores were calculated from 1 to 7 by summation of each involved region. We compared the patient, tumor, and metastatic characteristics according to the histological subtypes, and examined clinical outcomes. Results: The enrolled study cohort comprised 81% (n=346) Adenoca patients and 19% (n=81) SQ patients. The median age of the study population was 65 years (range, 30–94 years), and 263 (61.6%) patients were male. The most common metastatic sites were thoracic lymph nodes (LNs) (84.3%), followed by lung to lung/lymphangitic spread (59%) and bone (54.8%). The distribution of patient characteristics revealed that age 65 years (69.1% vs 50.6%; P=0.003) and male sex (84% vs 56.4%; P=0.001) were more frequently found in SQ patients. Regarding metastatic features, bone metastasis (60.4% vs 30.3%; P=0.001), lung to lung/lymphangitic metastasis (63% vs 42%; P=0.001), and brain metastasis (35% vs 16%; P=0.001) were significantly and more frequently found in Adenoca patients. Patients with high metastatic scores (score 3–6) were more frequently found to have Adenoca (91.6% vs 73.4%; P<0.001). In multivariate prognostic evaluation, sex (P<0.001), age (P=0.001), histology (P=0.001), LN status (P=0.032), pleural/pericardial metastasis (P=0.003), abdomen/pelvis metastasis (P=0.001), axilla/neck metastasis (P=0.006), and treatment factors (P=0.001) remained independent prognostic factors affecting overall survival. Conclusion: We observed distinctive patterns of primary metastases and clinical outcomes according to the histological subtypes in stage IV NSCLC. Future studies need to disclose the underlying mechanism of these unique metastatic features and tumor biologies.

Keywords: Adenocarcinoma, Squamous cell carcinoma, Metastases, lung cancer
P1.06-026 ADENOSQUAMOUS CARCINOMA OF THE LUNG: A SINGLE INSTITUTION EXPERIENCE IN THE ERA OF MOLECULAR TESTING

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Hematology and Oncology, Merit Health Biloxi, Biloxi/MS/United States of America

Background: Adenocarcinoma (ADC) is the most common subtype of non-small cell lung cancer (NSCLC) that compromises 0.4-4% of all lung cancers and is thought to carry a worse prognosis than adenocarcinoma (AD) or squamous cell carcinoma (SC). Epidermal growth factor receptor (EGFR) and Anaplastic Lymphoma Kinase (ALK) mutations have been observed in patients (pts) with this rare subtype. In the recent years EGFR tyrosine kinase inhibitors (Geftinib, Afatinib and Erlotinib) and ALK inhibitors (Ceritinib, Gilteritinib and Ceritinib) have prolonged progression free survival in high-stage adenocarcinomas of the lung. The current NCCN guidelines recommend EGFR and ALK mutation testing in metastatic ADC lung cancer patients. However the frequency of these mutations as well as outcomes of patients with ADC lung is not known in this era of targeted therapies. Methods: We retrospectively identified all pts seen in our oncology clinic for ADS during the last 10 years (1/2005 - 1/2015). Overall survival (OS) was estimated by Kaplan-Meier method Results: 16 pts were identified, median age at diagnosis was 77y (52-85y), 63% male, 81% had a smoking history, 87% had ECOG performance status 0; 37% had stage I, 18% had stage II, 18% had stage III and 25% had stage IV disease at diagnosis, 13% developed metastatic disease after treatment for stage III disease. 75% of pts diagnosed with metastatic disease after 2012 were tested for EGFR and ALK, while none diagnosed prior to 2012 were tested. All pts were negative for EGFR and ALK mutations. All pts with Stage I and II received only surgery; pts with stage IIIGO mulitymodality treatment with chemotherapy, radiation, and surgery. All pts with metastatic disease received chemotherapy, with regimens similar to those for AD or SC of lung. The median OS for pts with localized disease was 48.3 months (48.0-NA). The median OS for pts with metastatic disease was 5.4 months (2.3-9.2) Conclusion: Our small analysis showed that pts with localized ADC of lung had similar outcomes to those of historical pts with localized AD or SC of lung. However, pts with metastatic ADC of the lung had worse outcomes than historical pts with metastatic AD or SC of the lung even with similar chemotherapy regimens. Few pts had EGFR and ALK testing, but this is becoming more routine as we have better targeted therapies if they carry mutation.

Keywords: Targeted Therapies, adenosquamous carcinoma, Anaplastic Lymphoma Kinase (ALK) mutations, Epidermal growth factor receptor (EGFR) mutations

P1.06-027 RETROSPECTIVE STUDY OF TREATMENT FOR POSTOPERATIVE LOCAL RECURRENTITY OF LUNG CANCER

Kenjiro Tsuruoka, Keiji Miyoshi, Ninsu Matsunaga, Takahiko Nakamura, Shuhei Yoshida, Yousuke Tamura, Masafumi Imanishi, Soichiro Ikeda, Yasuhiko Fujisaka, Iigo Goto

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Background: There is no consensus regarding the standard treatment for postoperative local recurrence of lung cancer. In order to clarify the impact of differences in treatment on patient survival, we conducted a retrospective study of treatment outcomes for patients with postoperative local recurrence of lung cancer. Methods: The subjects of this study were patients who were diagnosed with postoperative local recurrence of lung cancer and treated at our hospital from 2008 to 2014. We divided patients according to treatment regimen, and compared patient characteristics and survival. Results: This study included 38 patients. Among them, 8 received radiation therapy (RT), 10 received chemoradiation therapy (CRT), 18 received chemotherapy (CT), and 2 received best supportive care. The patient characteristics were as follows:

- median age, range (71 years), 75 (55–84); gender male/female, 30/8; pStage at operation IA/IB/IIA/IIIB/IIIA/IIIB, 5/9/6/8/5/7; histology small cell carcinoma/ squamous cell carcinoma/adenocarcinoma, 5/12/21. There were no significant differences in patient characteristics between each treatment group. The proportion of patients who experienced disease progression after treatment was 75.0% (6/8) in the RT group, 20.0% (2/10) in the CRT group, and 77.8% (14/18) in the CT group. Progression free survival (PFS) tended to be better in the CRT group than in the other treatment groups. The differences in median PFS (months) were: RT vs CRT, 8.0 vs 15.5, HR=0.210 (95%CI 0.041-0.324), P=0.057; CRT vs CT, 5.5 vs 14.0, HR=0.206 (95%CI 0.047-0.908), P=0.037. Conclusion: In patients with postoperative local recurrence of lung cancer, CRT yielded better outcomes than the other treatments in terms of PFS. Keywords: postoperative, recurrence, relapse, local
Neuroendocrine 11%. Metastasis: Liver 79%, Bones: 72%; Adrenal: 37%; Lung: 35%; Brain: 23% of pts. CBs included: hypertension, diabetes, heart disease, dyslipidemia, COPD, hyperthyroidism, osteoporosis, Parkinson and dementia in 81, 68, 56, 52, 42, 14 and 6% of pts. In Group B had 3 comorbidities more often (59% vs 42%), p(0.05).

### Symptomatic Signs at Presentation

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Group A</th>
<th>Group B</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemoptysis</td>
<td>163(78)%</td>
<td>78(74)%</td>
<td>85(83)%</td>
</tr>
<tr>
<td>Cough</td>
<td>69(33)%</td>
<td>35(33)%</td>
<td>34(33)%</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>60(22)%</td>
<td>22(21)%</td>
<td>38(37)%</td>
</tr>
<tr>
<td>Chest discomfort</td>
<td>42(16)%</td>
<td>17(16)%</td>
<td>29(28)%</td>
</tr>
<tr>
<td>Cervical lymphadenopathy</td>
<td>38(18)%</td>
<td>18(17)%</td>
<td>20(19%)</td>
</tr>
<tr>
<td>SVC</td>
<td>27(13)%</td>
<td>12(11)%</td>
<td>15(15%)</td>
</tr>
<tr>
<td>Pancoast tumors</td>
<td>9(4%)</td>
<td>4(4%)</td>
<td>5(5%)</td>
</tr>
</tbody>
</table>

Results: Four pts (4.5%) mutated received TKI ± chemotherapy (Paclitaxel, Carboplatin, Bevacizumab) and are still in PR for 12+, 14+, 14+, 32+, 12+ months respectively. In 40 selected pts (≥ 80 yrs, PS = 3) a brain metastases + ≤ 2 Cs b weight loss ≥ 7% single agent was given. RR in 44% with mPFS 7(3–12) mo, mOS 19(16–23)mo. The rest received 3 cycles of chemo ± brain RT + GCSF support: ORR: 56% in A and 49% in B. mPFS: 9(3–18) mo and mOS 18(3–56) mo, 17(3–56) A. In 16 (3–44) in B. RR was 16% and 28% for pts 20/1 vs 2.5, p<0.01. In 720 cycles (410 and 310 in A and B), toxicity grade ≥ III: Febrile neutropenia in 11 vs 13 cycles, p =0.011, Anemia in 23 vs 27%, p<0.5, Thrombocytopenia in 25 vs 30%, p =0.5, Mucositis in 11 vs 15%, p = NS. Conclusion: 1: When indicative CT should be given, without reduction. 2: Haemoptysis and chest discomfort are common in older pts. 3: Febrile neutropenia was the main serious side effect. 4: GCSF prophylaxis is necessary. 5: In selective patients ≥ 80y single agent seems beneficial in second line.

Keywords: NSCLC, chemotherapy, elderly, Advanced, METASTATIC

**POSTER SESSION 1: P.06.00 ADVANCED NSCLC & CHEMOTHERAPY/IMMUNOTHERAPY ADVANCED GENERAL – MONDAY, DECEMBER 5, 2016**

**P.06-030 EXTENDED LYMPH NODE DISSECTION THROUGH MEDIUM STERNOTOMY IN N3 LEFT NSCLC SURGICAL RESULTS AND ANATOMICAL FINDINGS**

**Shingo Ikeda**, Toshiya Yokota, Tatsuya Hoshino, Takashi Sakai
Surgical Department of Respiratory Center, Mitsu Memorial Hospital, Tokyo/Japan

Background: The role of surgical approach to stage IIIA or IIIB disease surgery has not been considered appropriately. Patients with mediastinal lymph node metastasis have a poor prognosis, especially for N3 (contra lateral lymph node metastases) cases. We performed neck and bilateral mediastinal lymph node dissection by medium sternotomy to resect lung cancer and dissect the bilateral mediastinal lymph nodes. Methods: An extended surgical approach to bilateral neck mediastinal and nodal dissection based on the knowledge about the pathways of lymph drainage, systemic neck and bilateral mediastinal nodal dissection through a median sternotomy, beyond the anatomical difficulties would bring some improvement on the survival of the patients with N3 left NSCLC without any preoperative treatments routinely. Results: Patients with n = 304 and N3 (neck lymph node metastases case) cases have poor prognosis, and lung operation is not typically indicated. We performed neck and bilateral mediastinal lymph node dissection by medium sternotomy to resect lung cancer and dissect the bilateral mediastinal lymph nodes. We have performed this operation in 289 patients with primary left lung cancer excluding small cell carcinoma and stageIV since 1987. 42 patients had n = 3 lymph node metastases. We will report the investigation of the prognostic of left NSCLC patients who underwent initially our extended neck and bilateral mediastinal dissection, focused on the patients with N3 disease. According to the macroscopic dissection procedure, dissection of the lymphatics from the lungs to the supraclavicular lymph nodes was performed by sequential removal of the related organs. We systematically compared and reviewed the route of lymphatic communications to the neck and contra lateral side with the anatomical significance of left-to-right lymphatic communications in the bilateral mediastinal lymph nodes. The 5-year survival rate (Kaplan-Meier method), including operative deaths and deaths due to unrelated diseases, was 48.8% in n = 289 patients in N3. Conclusion: We found various lymphatic metastases pattern such as between neck and mediastinal lymph nodes and around the trachea in terms of clinical and anatomical status.

**P.06-032 THE HUMANISTIC BURDEN OF ADVANCED NON-SMALL CELL LUNG CANCER PATIENTS IN EUROPE - A REAL WORLD SURVEY**

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1Adelphi Real World, Bollington/United Kingdom, 2Bristol-Myers Squibb, Unibridge/United Kingdom, 3Bristol-Myers Squibb, Rueil-Malmaison/France

Background: Previous publications have demonstrated that advanced Non-Small Cell Lung Cancer (aNSCLC) patients have worse HRQoL compared to the general population. Few publications have focused on the impact of aNSCLC on activities of daily living and the humanistic burden incurred by different groups of aNSCLC patients in the real world setting. Methods: Data were taken from a multi-center, cross-sectional study of aNSCLC patients conducted in France, Germany and Italy. The study consisted of three components: medical chart review, patient questionnaire and caregiver questionnaire. Overall, 683 consulting patients were recruited via treating physicians. Patients’ health state was quantified using the EuroQoL-5D (EQ-5D-3L) comprising of five domains: mobility, self-care, ability to perform usual activities, pain, anxiety and depression) and the burden on HRQoL quantified using the EuroQol questionnaire for Research and Treatment of Cancer Quality of Life.
Life Questionnaire (EORTC QLQ-C30), a 30 item questionnaire yielding five functional scales, three symptom scales, a global health status/QoL scale, and six single items. Analysis was stratified by patients’ line of therapy. Statistical significance was assessed using Mann-Whitney U tests. Results: Patients’ mean (SD) age was 65.2 (9.7), 68.8% were male and 89.0% had stage IV NSCLC. Over two-thirds (71%) of patients were receiving 1st line advanced therapy, whilst 29% were receiving later lines of therapy. Regarding histology, 74% of patients were non-squamous compared to 26% squamous. The mean EQ-5D-3L index for 2nd line or later patients was significantly lower compared to patients on 1st line treatment (0.57 vs 0.65; p=0.002). Three domains showed significant decreases: mobility, self-care and ability to perform usual activities. In terms of EORTC scores, patients on later lines of treatment experienced a lower overall global health status (QL2) compared to 1st line patients (43.8 vs 50.7; p<0.001). Significant differences were also observed in all other EORTC scales except for diarrhoea. Conclusion: 1st line aNSCLC patients have a diminished health state in comparison to the general population (EQ-5D scores 0.65 vs 0.78). In addition compared to other cancer sufferers, aNSCLC patients have a worse QoL (QLQ-C30 QL2 score 48.8 v 61.5 for stage IIIb/IV cancer patients). The real world study showed that both health status and QoL significantly worsened with advancement to later lines of treatment. The results show a high unmet need for more effective 1st line treatments to prevent disease progression while maintaining patient quality of life.

Keywords: NSCLC, humanistic burden, quality of life, Real world

S354


P1.06-033 NON-SMALL CELL LUNG CANCER IN YOUNG PATIENTS: CLINICO-PATHOLOGIC CRITERIA AND PROGNOSTIC FACTORS

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Background: A cancer registry was analyzed to determine the clinicopathologic characteristics and prognosis of non-small cell lung cancer (NSCLC) in patients <45 years of age. We report survival data of patients less than 45 years old undergoing surgical intervention at the National Cancer Institute over a period of 15 years. Patients and methods: Among enrolled NSCLC cases attending National Cancer Institute – Cairo (NCI) between 2000 and 2015, we retrospectively reviewed those who were <45 years old. Data regarding demographics, ECCOG-performance status (PS), histology, grade, stage, chemotherapy type, number of cycles, overall and progression-free survival (OS, PFS) were obtained. Pearson’s (X2) test, Cox regression and Kaplan-Meier survival curves were used for statistical analysis. Results: Among 99 NSCLC cases, we identified 22 cases ≤45 years. Lower stages were more prevalent among young (77.3%) versus old group (54.5%); p=0.05. Median OS in young versus old group was 18 versus 15 months (p=0.773), while PFS was 4 versus 6 months respectively (p=0.322). In our subgroup analysis (n=22), median age was 42 years (30-45 years), Nearly three-quarters were males, 40% were PS ≥2. The majority of cases in young group were stage IIIb (77.3%). Pathology was squamous (40.9%), adenocarcinoma (22.7%), undifferentiated (22.7%) and adenosquamous carcinoma in 4.5% of our cases. Median OS and PFS was 18 and 4 months respectively. Significant difference in OS and PFS was observed among responder versus non-responders in multivariate analysis (Figure). Conclusion: Good response to chemotherapy is the best way to prolong survival among young NSCLC cases irrespective of PS, gender, stage or pathology.

Keywords: NSCLC, advanced age, National Cancer Institute, Young age, Response to chemotherapy

P1.06-034 OUTCOMES AFTER PULMONARY METASTASECTOMY FOR METASTATIC CANCER

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Background: In most malignant diseases, the ability to constantly metastasize remains a truly challenging obstacle in cancer patients. Historically in the past, any local surgical treatment in patients with systemic malignant disease is considered without any prognostic benefit, this has since evolved with many studies confering huge success rates with excellent prognostic benefits. We hereby report our experience over the last 10 years at Wellington Regional Hospital, Cardiothoracic unit. Methods: A retrospective study was undertaken in series of patients with colorectal, melanoma, breast, sarcoma & renal metastatic disease undergoing pulmonary metastasectomy, from year 2000 to 2010. These data was identified & stratified into groups using hospital patient database & ORSOS theatre database with the aid of Excel spreadsheet. Results: All these patients were operated on either – unilateral versus bilateral, VATS or thoracotomies with or without lymph node dissection as well as repeat surgeries. The role of metastasectomy in their treatment options & the prognostic factors with impact on survival discussed. Conclusion: In carefully selected surgical patients, pulmonary metastasectomy for metastatic diseases confers continual prognostic survival advantage for these patients.

Keywords: pulmonary metastasectomy, Metastatic Disease, outcomes

P1.06-035 FREQUENCY AND CLINICAL RELEVANCE OF EGFR-MUTATIONS AND EML-ALK-TRANSLOCATIONS IN OCTAGENERIANS WITH NSCLC

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Background: Novel therapies targeting genetic alterations have improved response rates and overall survival for some patients with NSCLC; however, only a minority of caucasian patients with lung cancer benefit from these treatments. Testing for EGFR mutation and ALK translocation is recommended for all patients with advanced adenocarcinoma, but the highest occurrence of these driver mutations has been described in
Background: The aim of this retrospective study was to review recurrence patterns of stage I non-small cell lung cancer (NSCLC), and to identify prognostic factors for post-recurrence survival (PRS). Methods: Among 940 patients with pathological stage I NSCLC who had undergone curative resection between 2001 and 2009, total 261 patients who had experienced recurrence were included in this study. Number of patients with adenocarcinoma (ADC) were 188, squamous cell carcinoma (SCC) were 62. Oligo-recurrence was defined as 1-3 loco-regional or distant recurrent lesions restricted to a single organ. Potentially-curative local treatment (PCLT) included surgery, stereotactic radiotherapy (SRT), and photodynamic therapy (PDT). Results: Median follow-up duration was 65 months (range, 4-180 months) and median disease-free interval (DFI) was 23 months (range, 2-95 months). A total of 46 patients received oligo-recurrence were lung in 84 patients, followed by brain in 18 patients, bronchial stump in 18, and single-station of mediastinal lymph nodes in 12. Local treatment for recurrent tumor included surgery in 59 patients, SRT in 50, PDT in 2, and other radiotherapy in 53. Seventy-four patients received chemotherapy only, and 36 patients took conservative treatment. Among 125 patients who were evaluated for EGFR gene mutation study, positive results was detected in 62 patients, and 31 patients were found to have EML4-ALK translocations and 2 patients were found to have EGFR mutation (1 Del31, 1 L858R). This represents a 71% frequency of treatable driver mutations in octogenarians with non-squamous NSCLC. Rates of genetic drivers were somewhat lower, but still clinically relevant, in non-squamous NSCLC patients aged 70-74 (27.0%) and 75-79 (26.7%). Conclusion: Very elderly patients (80 years of age) with non-squamous NSCLC were found to have high rates of the driver alterations EGFR mutation and ALK translocation. This is clinically relevant, as this often frail and comorbid population may not be suitable for treatment with cytotoxic chemotherapy and may benefit from first line treatment with a targeted tyrosine kinase inhibitor. Testing for these genetic alterations should not be restricted to younger patients. The biology of lung cancer in the very elderly may differ from that of moderately elderly patients, as the longevity of these patients may select for individuals more resistant to, or with little exposure to, environmental carcinogens.

Keywords: EGFR, EML4-ALK, elderly, NSCLC

P1.06-036 POST-RECURRENCE SURVIVAL ANALYSIS OF STAGE I NON-SMALL CELL LUNG CANCER: PROGNOSTIC SIGNIFICANCE OF LOCAL TREATMENT

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Department of Thoracic and Cardiovascular Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

Background: Background of this study was to review recurrence patterns of stage I non-small cell lung cancer (NSCLC), and to identify prognostic factors for post-recurrence survival (PRS). Methods: Among 940 patients with pathological stage I NSCLC who had undergone curative resection between 2001 and 2009, total 261 patients who had experienced recurrence were included in this study. Number of patients with adenocarcinoma (ADC) were 188, squamous cell carcinoma (SCC) were 62. Oligo-recurrence was defined as 1-3 loco-regional or distant recurrent lesions restricted to a single organ. Potentially-curative local treatment (PCLT) included surgery, stereotactic radiotherapy (SRT), and photodynamic therapy (PDT). Results: Median follow-up duration was 65 months (range, 4-180 months) and median disease-free interval (DFI) was 23 months (range, 2-95 months). A total of 46 patients received oligo-recurrence were lung in 84 patients, followed by brain in 18 patients, bronchial stump in 18, and single-station of mediastinal lymph nodes in 12. Local treatment for recurrent tumor included surgery in 59 patients, SRT in 50, PDT in 2, and other radiotherapy in 53. Seventy-four patients received chemotherapy only, and 36 patients took conservative treatment. Among 125 patients who were evaluated for EGFR gene mutation study, positive results was detected in 62 patients, and 31 patients were found to have EML4-ALK translocations and 2 patients were found to have EGFR mutation (1 Del31, 1 L858R). This represents a 71% frequency of treatable driver mutations in octogenarians with non-squamous NSCLC. Rates of genetic drivers were somewhat lower, but still clinically relevant, in non-squamous NSCLC patients aged 70-74 (27.0%) and 75-79 (26.7%). Conclusion: Very elderly patients (80 years of age) with non-squamous NSCLC were found to have high rates of the driver alterations EGFR mutation and ALK translocation. This is clinically relevant, as this often frail and comorbid population may not be suitable for treatment with cytotoxic chemotherapy and may benefit from first line treatment with a targeted tyrosine kinase inhibitor. Testing for these genetic alterations should not be restricted to younger patients. The biology of lung cancer in the very elderly may differ from that of moderately elderly patients, as the longevity of these patients may select for individuals more resistant to, or with little exposure to, environmental carcinogens.

Keywords: EGFR, EML4-ALK, elderly, NSCLC

P1.06-038 SURVIVAL AND PROGNOSTIC FACTORS OF OLIGOMETASTATIC NON-SMALL CELL LUNG CARCINOMA: A SINGLE CENTER EXPERIENCE

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Background: Background: In patients without targeted mutations platinum-based chemotherapy is still current treatment method with a median survival rates of 8-11 months. Patients with single side oligo-metastatic disease should be consider for curative aggressive therapies for both primary and metastatic sides for better survival (NCCN 2016). Methods: Totally 19 oligo-metastatic NSCLC patients were evaluated retrospectively by using hospital database. All patients had single metastatic side. Results: Among 19 eligible patients there was male predominance (n=16, 84.2%). Eight patients had co-morbidities requiring regular medication. Histopathological, there were 13 (68.4%) adenocarcinoma and 6 (31.6%) non-adenocarcinoma. While brain was the most common site for metastasis (10, 52.6%), it was followed by bone (n=6, 31.6%). Treatments for primary tumour side were surgery (n=6, 31.6%), concurrent CRT (n=5, 26.3%) and systemic drugs (n=8, 42.1%). Median follow-up for whole cases were 59.1 weeks. Median overall survival (OS) and progression free survival (PFS) were 140 (±33.7) and 76 (±24.2) weeks respectively. Progressions were observed mostly in 45.4. week. Univariate cox regression analyses for OS and PFS is indicated in Table 1. Clinical T and N staging had significant relation with OS (P<0.02 and 0.03 respectively).

Keywords: recurrence, Oligometastasis, lung cancer
There was no relationship between bone or brain metastasis and histopathology, gender, clinical T and N staging. Median survival after first progression (SAPF) was 63 weeks (±59.17). Among study parameters only clinical T staging had significant relation with SAPF (p = 0.026). Median SAPF was better in patients with progression of distant metastasis (p < 0.05).

<table>
<thead>
<tr>
<th>Factor</th>
<th>OS</th>
<th>PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hazard Ratio</td>
<td>p</td>
<td>Hazard Ratio</td>
</tr>
<tr>
<td>Age (cut-off = 65)</td>
<td>1.034 (0.18-5.1)</td>
<td>0.96</td>
</tr>
<tr>
<td>Co-morbidity</td>
<td>2.3 (0.54-9.8)</td>
<td>0.24</td>
</tr>
<tr>
<td>Brain Metastasis</td>
<td>0.88 (0.21-3.6)</td>
<td>0.86</td>
</tr>
<tr>
<td>Histopathology (adeno vs non-adeno)</td>
<td>0.22 (0.03-1.4)</td>
<td>0.10</td>
</tr>
<tr>
<td>Bone Metastasis</td>
<td>1.78 (0.43-7.31)</td>
<td>0.42</td>
</tr>
<tr>
<td>pN Staging (n0 and N1-2)</td>
<td>0.12 (0.173)</td>
<td>0.21</td>
</tr>
<tr>
<td>cT Staging</td>
<td>2.17 (1-4.7)</td>
<td>0.02</td>
</tr>
<tr>
<td>cN Staging (n0 and N1-2)</td>
<td>2.3 (0.86-6.6)</td>
<td>0.03</td>
</tr>
<tr>
<td>Non-surgical curative treatment</td>
<td>1.88 (0.81-4.5)</td>
<td>0.42</td>
</tr>
<tr>
<td>Surgery</td>
<td>0.31 (0.016-1.65)</td>
<td>0.14</td>
</tr>
</tbody>
</table>

Conclusion: Even oligo-metastatic NSCLC means stage 4 of disease, currently treatment approaches for both primary and metastasis sides can increase patients’ prognosis than other stage 4 cases. Similar to the existed retrospective studies we had OS more than 2 years and PFS more than 1year.

Keywords: Oligometastasis, nonsmall cell lung cancer, survival

P1.06-039 RETROSPECTIVE STUDY OF THE INCIDENCE AND OUTCOMES FROM LUNG CANCER THAT DEVELOPED FOLLOWING A SOLID ORGAN TRANSPLANT

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Background: Organ transplant recipients (OTR) have an increased risk of developing post-transplant malignancies with lung cancer being one of the most common. We investigated incidence and outcomes of lung cancer in OTR managed at the University Health Network. Methods: The study population, patient characteristics, treatments and outcomes were summarized from solid OTR databases, our cancer registry and patient charts from January 1, 1989 to December 31, 2015. Univariate Kaplan-Meier curves estimated overall survival (OS) by histology, stage and chemotherapy. Results: Amongst 7994 OTR (heart [N=765], lung [n=1668], liver [n=238], kidney [n=3273]), 123 overall survival (OS) by histology, stage and chemotherapy. Results: Amongst 1,1980 to December 31, 2015. Univariate Kaplan-Meyer curves estimated

P1.06-040 HOME-BASED PULMONARY REHABILITATION IN ADVANCED NON SMALL CELL LUNG CANCER PATIENTS TREATED BY ORAL TARGETED THERAPY: A FEASIBILITY STUDY

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Background: Pulmonary rehabilitation (PR) is valuable in the peri-operative setting of non small cell lung cancer (NSCLC) patients, but not established for stage IIIB-IV disease. Previously, we showed that home-based PR is feasible and may significantly improve quality of life (QoL) and functional status of NSCLC patients treated by chemotherapy (submitted). The goal of this study was to assess the feasibility and value of home-based PR in advanced NSCLC patients treated by oral targeted therapies. Methods: Advanced NSCLC patients with oral targeted therapy were recruited in a prospective study in 2015-2016 in Lille University Hospital, France. After written informed consent, they benefited from 8 weeks home-based PR including functional exercises, psychological and nutrition support, therapeutic education. Exclusion criteria were cardiovascular contraindication to PR, symptomatic brain metastasis, bone metastasis with high fracture risk, or severe cognitive disorder. Main endpoints were adherence, inclusion rate, and cause of refusal. Secondary endpoints were PR benefits assessed by QoL scales (EORTC QLQ C30, FACT-L, HAD). Functional capacity: 6min walk test, 6 min stepper test, spirometry, respiratory muscle strength; and global condition: nutrition, treatment tolerance. This study was approved by local Ethical Committee Results: Among 36 screened patients, the adhesion rate was 55.6% with 20 patients joining the study. Other patients refused mostly because (a) of “lack of interest for PR and they don’t want to be disturbed” (40% of cases), or (b) they considered “their physical activity already sufficient” (12%), or (c) “family constraints” (12%). Only 15 patients (41.6%) started PR (3 early deaths, 1 exclusion for intraventricular thrombosis), 1 consent withdrawal. No serious adverse event was reported but only grade 1 asthenia or musculoskeletal pain. Significant increases of FACT-L score from 84.7 to 100.2 (p=0.02) and 6 min stepper test from 140 to 195.7 steps (p=0.01) were found after PR, and preservation of patients’ autonomy reflected by stability of 6WT data. Most of other parameters exhibited a positive but not significant trend, likely due to the limited number of participants. Conclusion: Home-based PR is feasible and well-tolerated in patients with advanced NSCLC treated by oral targeted therapies. Significant improvements were obtained with PR based on 6ST and QoL FACT-L data. Moreover, PR was highly appreciated by patients, their relatives, and all medical teams raising our will to be able to propose PR to
all our stage III-IV NSCLC patients. Currently, this study is still ongoing and multicentric, aiming at recruiting 50 extra patients.

Keywords: NSCLC, pulmonary rehabilitation, Targeted therapy, supportive care

POSTER SESSION I. P1.06: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/IMMUNOTHERAPY ADVANCED GENERAL - MONDAY, DECEMBER 5, 2016

P1.06-041 OVERALL SURVIVAL AND INTERMEDIATE OUTCOMES AMONG SCANDINAVIAN NON-SMALL CELL LUNG CANCER PATIENTS: THE SCAN-LEAF STUDY

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Background: The past decade has seen several advances in the field of non-small cell lung cancer (NSCLC), with improved tools for tumor characterization as well as novel targeted and immune therapies. It is important to understand the current treatment landscape including treatment outcomes, in order to maximize patient benefits from these advances. SCAN-LEAF is a Scandinavian retroperspective cohort study with prospective annual data cuts, providing a unique opportunity for insights into real-world clinical NSCLC practice over more than a decade. It includes clinical practice patterns of tissue biopsy, pathological diagnosis and tumor biomarker status testing, and their relationship to treatment choices and outcomes. Here, we present intermediate and survival outcomes by disease stage and histology subtype, and factors associated with survival. Methods: SCAN-LEAF consists of a registry-based cohort including all diagnosed NSCLC patients in Denmark, Norway and Sweden (Cohort 1), and a Swedish sub-cohort (Cohort 2) supplemented by data from electronic medical records (EMRs). Based on the first data collection including data from NSCLC patients diagnosed 2005-2013, overall survival (OS; Cohort 1 & 2) and progression-free survival (PFS; Cohort 2) will be estimated using Kaplan-Meier analysis and reported as cumulative incidences (with 95% CI) by disease stage at diagnosis, histological subtype, biomarker status, presence of metastases, age and gender. Response rates (Cohort 2) will be described by treatment line in addition to stage and histology subtype. Association of stage with survival (Cohort 1 & 2) and treatment response (Cohort 2) will be analyzed by Cox regression with time to event (death or response) as outcome variable and disease stage category at diagnosis, follow-up time, and therapy line as stratification variables. In addition, the relationship between OS and intermediate outcomes, as well as predictors of OS (e.g. smoking and biomarker status, lesion location, metastasis at diagnosis), will be explored by Cox regression (Cohort 2).

Results: Intermediate and survival outcomes for Scandinavian NSCLC patients diagnosed between 2005 and 2013, as well as any association between overall survival and factors such as patient characteristics and treatment patterns, will be presented. Conclusion: The SCAN-LEAF study, expected to include >115,000 Scandinavian NSCLC patients and >2,000 sub-cohort patients diagnosed between 2005 and 2016 during the full duration of the study, will give valuable insights into current care, changing treatment patterns and patient outcomes in a real-world setting. A better understanding of factors giving valuable insights into current care, changing treatment patterns and will inform clinical decision-making.

Keywords: Progression-free survival, epidemiology, non-small cell lung cancer, survival

POSTER SESSION I. P1.06: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/IMMUNOTHERAPY ADVANCED GENERAL - MONDAY, DECEMBER 5, 2016

P1.06-042 THE IMPORTANCE OF MEDICATION RELATED OSTEONECROSIS OF THE JAWS (MRONJ)

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Background: Medication related osteonecrosis of the jaws (MRONJ) is an increasing problem globally, which may lead to loss of teeth and jaw bone and has a significant impact on quality of life. MRONJ is known since 2003, reported after antiresorptive treatment with bisphosphonate, and since 2010 also from Denosumab for skeletal metastases from breast cancer, prostate cancer and multiple myeloma. Recently, MRONJ has also been related to chemotherapy, including Tyrosine Kinase Inhibitors for lung cancer, kidney cancer and gastrointestinal cancer without skeletal metastases. The onset of MRONJ is often precipitated by one of the above medication types in combination with a tooth extraction. Therefore it is recommended that all patients have a dental screening and relevant dental treatment before the start of medication with antiresorptives (bisphosphonates/denosumab) or Tyrosine Kinase Inhibitors. The purpose of this study is to raise awareness that MRONJ can be prevented and that MRONJ also occurs among patients receiving chemotherapy without bisphosphonates or denosumab. Methods: Rigshospitalet established the Copenhagen ONJ Cohort of consecutive patients with MRONJ since 2004, and have performed systematic prospective data collection since 2010. Results: Among 247 patients enrolled in the Copenhagen ONJ Cohort 163 received treatment with bisphosphonates in 109 cases and denosumab in 54 cases. In addition, since 2013 we have received 7 patients with MRONJ from Tyrosine Kinase inhibitors. In 85 out of 163 cancer patients (52%) the onset of MRONJ was related to tooth extraction. Conclusion: More than 50% of the MRONJ cases could potentially be avoided. If all patients had dental examination and had repaired or extracted bad teeth before start of antiresorptive medication, thus all cancer patients should have dental examination before start of medical treatment.

Keywords: Chemotherapy jaw necrosis Prevention of Jaw necrosis
P1.06-044 COSTS OF ADVERSE EVENTS (AE) ASSOCIATED WITH CANCER THERAPIES IN NON-SMALL CELL LUNG CANCER (NSCLC) IN FRANCE

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Background: The lung cancer is a cancer of the most in Japan and first place seen, four appear to have an important economic impact, with a management cost of at least €3,000 per event.

Methods: We intended for multiple neoplasms 339 cases including hematological malignancies. Among them, 7 did not have cost data available in the literature. Three French oncology experts were consulted. Questionnaires were sent before the meeting with the experts, asking for, according to the grade, insight on resource use (hospitalisation, follow-up visits, diagnosis exams, treatments).

Results: The mean AE cost was €206 for thrombocytopenia, €263 for ocular toxic effect, €2,332 for arthralgia, €3,282 for venous thromboembolism, €3,732 for pulmonary bleeding, €5,176 for dehydration, €5,751 for pneumonia, infection or pneumonitis. Hospitalisation costs corresponded to 46% to 100% of total AE cost. These AE costs were consistent with the costs of other grade 4 AEs previously published for NSCLC therapies. Conclusion: Among seven grade 3 and 4 AEs seen, four appear to have an important economic impact, with a management cost of at least €3,000 per event.

Keywords: cost, adverse events, Health Economics, NSCLC

P1.06-045 MULTIPLE NEOPLASMS CONSIST OF LUNG CANCER AND HEMATOLOGICAL MALIGNANCIES

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Background: The lung cancer is a cancer of the most in Japan and first place in cause of death. Lung cancer (LC) is still poor prognosis disease that cure only in early clinical stage. We report that we reviewed 55 cases of multiple neoplasms with lung cancer and the hematological malignancies. Methods: We intended for multiple neoplasms 339 cases including hematological malignancies. We reviewed 55 cases of multiple neoplasms consisting of lung cancer and hematological malignancies.

Results: All patients were included in clinical trials. A dose reduction was reported in 41% of therapeutic agent (II line TKI 20%, IT 31%; III line TKI 33%, IT 27%). 31% of pts were treated with antiangiogenic drugs. Immunotherapy (IT) was administered in 16% of all treated pts. 7% of pts received only BSC. Second- and third-line treatment were given to 44% and 8% of pts, respectively. 5% of pts who received second line treatment and 60% of pts treated with a third line therapy had a novel therapeutic agent (II line TKI 20%, IT 31%; III line TKI 33%, IT 27%). 31% of pts were included in clinical trials. A dose reduction was reported in 41% of therapies and the discontinuation rate was 9%. Survival data are not mature at this time. Conclusion: Our data, albeit preliminary, suggest an evolution in the management of NSCLC in the elderly. The interesting activity and the good safety profile encourage the use of novel agents also in this setting of NSCLC. Keywords: elderly, Advanced non small cell lung cancer, Targeted therapy, Immunotherapy

P1.06-046 CAN WE BETTER MANAGE ADVANCED NSCLC IN THE ELDERLY WITH THE NEW THERAPEUTIC AGENTS? PRELIMINARY ANALYSIS OF A REAL-LIFE MULTICENTER STUDY

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Background: Systemic treatment of NSCLC has profoundly changed over the past years with novel therapeutic strategies recently implemented in clinical practice. Benefit of these novel agents in elderly patients (pts) is uncertain, given the paucity of prospective data in this population. Moreover, elderly pts are often undertreated, due to comorbidities and toxicity concerns. Therefore, we aimed to evaluate the access, safety and outcome with novel therapeutic agents in pts ≥70 years (pts).

Methods: We planned an observational study to retrospectively evaluate consecutive elderly patients (≥70 yrs) with metastatic NSCLC treated at 9 Italian Centers between January 2014 and December 2015. Data collected include clinical and pathological characteristics, treatment types, safety and outcome. Results: 220 patients with stage IV NSCLC were included in this preliminary analysis (53% IVA, 47% IVB). Median age was 74,5 (range 70-85) and 69% were male. 15% of pts aged 80 years or older. ECOG PS was 0, 1, 2 in 37%, 5% and 12% of pts, respectively. According to comprehensive geriatric assessment, 59% of pts were fit, 28% vulnerable and 13% frail. Histology was 23% squamous cell carcinoma, 72% non-squamous cell carcinoma and 5% NOS. EGFR mutation was diagnosed in 24% of cases, 1% and 17% of pts had ALK and ROS-1 translocations, respectively. 90% of pts received a systemic therapy: 48% a platinum doublet chemotherapy (CHT), 27% a mono-CHT, 25% an EGFR tyrosine kinase inhibitor (TKI). Only 1% of pts were treated with antiangiogenic drugs. Immunotherapy (IT) was administered in 16% of all treated pts. 7% of pts received only BSC. Second- and third-line treatment were given to 44% and 8% of pts, respectively. 5% of pts who received second line treatment and 60% of pts treated with a third line therapy had a novel therapeutic agent (II line TKI 20%, IT 31%; III line TKI 33%, IT 27%). 31% of pts were included in clinical trials. A dose reduction was reported in 41% of therapies and the discontinuation rate was 9%. Survival data are not mature at this time. Conclusion: Our data, albeit preliminary, suggest an evolution in the management of NSCLC in the elderly. The interesting activity and the good safety profile encourage the use of novel agents also in this setting of NSCLC. Adequate selection of elderly pts and personalized approach are still matters of debate. Use of adapted schedule and dose reduction could warrant a good compromise between safety and efficacy.

Keywords: elderly, Advanced non small cell lung cancer, Targeted therapy, Immunotherapy

P1.06-047 MANAGEMENT OF PATIENTS AGED OVER 70 YEARS WITH NEWLY DIAGNOSED LUNG CANCER

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Background: Lung cancer is an important cause of mortality and morbidity worldwide. It is the third most common cancer in the UK. Due to an increase in life expectancy there is an increase in the proportion of patients greater than 70 years being diagnosed with lung cancer. We looked at the management of patients diagnosed with newly diagnosed lung cancer over a period of 12 months in a large UK Teaching hospital. The main aim of this study was to compare the outcome of various treatment options offered to elderly patients diagnosed with lung cancer. Methods: All individuals diagnosed with lung cancer aged ≥70 years were enrolled in the study. Patients were referred from hospital. 50% were referred from GP. In terms of treatment; 52% received best supportive care (BSC), 30% surgery and 17% chemotherapy. Common reasons for patients referring refusal were poor performance status (65%), and comorbidities (6%), and poor quality of life (10%). 22% patients had chemotherapy improved survival compared to BSC, 5 v.s. 10 months. Node positivity was poor prognostic sign; median survival for NO, N1 and N2 were 17, 10, 5 and 3 months respectively Conclusion: Treating elderly patients with lung cancer is challenging because at the time of diagnosis the tumor is often advanced and furthermore elderly patients often suffer with multiple comorbidities which makes treatment more difficult. In our cohort, patients who received active ontological treatment had improved overall survival. Majority of the patients didn’t receive active ontological treatment due to poor performance status or co morbidities and hence not fit for treatment. Our data suggests that age should not be considered as a limiting factor for chemotherapy and there is a need for prospective studies to further evaluate active ontological management of older patients, since with careful selection this group can benefit from active treatment.

Keywords: lung cancer, elderly, chemotherapy, Best supportive care

Abstracts

P1.07-002 GT28, A CYCLIN DEPENDENT KINASE 4/6 INHIBITOR, IN COMBINATION WITH TOPOTECAN FOR PREVIOUSLY TREATED SMALL CELL LUNG CANCER: PRELIMINARY RESULTS

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Background: Chemotherapy-induced bone marrow and immune system toxicity causes significant acute and long-term consequences. GT28 is a potent and selective CDK4/6i (CDK4/6 inhibitor) in development to reduce chemotherapy-induced myelosuppression and preserve immune system function in small cell lung cancer (SCLC) patients. Hematopoietic stem and progenitor cells (HSPC) are dependent upon CDK4/6 for proliferation, and preclinical models demonstrated that transient GT28-induced G1 cell cycle arrest renders them resistant to chemotherapy cytotoxicity, allowing faster hematopoietic recovery, preservation of long-term stem cell and immune system function, and enhancement of chemotherapy anti-tumor activity. Methods: Objectives of this ongoing multicenter Phase Ib/2a study are to assess the dose limiting toxicities (DLTs), safety, hematological profile, PK, and anti-tumor activity of GT28 in combination with topotecan. The study consists of a limited open-label, dose-finding portion (Part 1; up to 40 patients) and an open-label, single-arm expansion portion (Part 2; 28 patients). Eligible patients had histologically/cytologically confirmed SCLC, adequate organ function, ECOG performance status 0-2, and were referred from GP. In terms of treatment; 52% received best supportive care (BSC), 30% surgery and 17% chemotherapy. Common reasons for patients referring refusal were poor performance status (65%), and co-morbidities (6%). 22% patients had chemotherapy improved survival compared to BSC, 5 v.s. 10 months. Node positivity was poor prognostic sign; median survival for NO, N1 and N2 were 17, 10, 5 and 3 months respectively Conclusion: Treating elderly patients with lung cancer is challenging because at the time of diagnosis the tumor is often advanced and furthermore elderly patients often suffer with multiple comorbidities which makes treatment more difficult. In our cohort, patients who received active ontological treatment had improved overall survival. Majority of the patients didn’t receive active ontological treatment due to poor performance status or co-morbidities and hence not fit for treatment. Our data suggests that age should not be considered as a limiting factor for chemotherapy and there is a need for prospective studies to further evaluate active ontological management of older patients, since with careful selection this group can benefit from active treatment.

Keywords: lung cancer, elderly, chemotherapy, Best supportive care

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1 P1.07-003 A PHASE II STUDY EVALUATING THE COMBINATION OF EVEROLIMUS WITH CARBOPLATIN/PACLITAXEL AS 1ST LINE TREATMENT IN PATIENTS WITH ADVANCED LCNEC

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Background: Approximately 3% of all lung cancers are made up of large cell neuroendocrine carcinoma of the lung (LCNEC). These tumors in general have a bad prognosis and currently there are only very limited treatment options, involving platinum derivatives and etoposide. The PI3AK/mTOR pathway is known to be dysregulated in neuroendocrine tumors (NETs). Since the mTOR inhibitor RAD001 (everolimus) already has proven effectiveness in different types of NETs, we tested whether everolimus might be also an effective treatment option in advanced LCNEC patients. Methods: In this multi-centre, phase II study, everolimus was combined with platinum-based chemotherapy in patients with histologically confirmed stage IV LCNEC according to WHO criteria. Further inclusion criteria were measurable disease according to RECIST 1.1 and adequate bone marrow, renal, and liver function. Exclusion criteria were symptomatic CNS metastases and prior treatment for advanced LCNEC. Enrolled patients received everolimus once a day in combination with 4 cycles of carboplatin and paclitaxel, followed by daily everolimus maintenance therapy. The primary objective was to evaluate the efficacy by assessing the proportion of progression-free patients after three months of treatment. Results: Ten German trial sites enrolled altogether 49 patients (mean age: 62 ± 9 years; 71% men). The primary endpoint (proportion of pts progression-free at month 3) was achieved by 24 patients (49%), assessed by an independent central imaging reviewer. Further efficacy evaluation showed an overall response rate (ORR) until month 3 of 45%, a disease control rate (DCR) until month 3 of 73.5%, a median progression-free survival (PFS) of 4.3 months, and a median overall survival (OS) of 9.8 months. At least one toxicity occurred in 86% of all enrolled patients with grade 3/4 toxicities in 51%. Most frequent toxicities were diarrhea, fatigue, anemia, and neutropenia. Conclusion: The results show that combining chemotherapy of carboplatin and paclitaxel with the mTOR inhibitor everolimus is an alternative treatment option for LCNEC patients. When comparing to other trials, the effectiveness is comparable to a treatment regimen of cisplatin and etoposide.

Keywords: LCNEC, Neuroendocrine tumor, Everolimus

POSTER SESSION 1: P1.07-003 A PHASE II STUDY EVALUATING THE COMBINATION OF EVEROLIMUS WITH CARBOPLATIN/PACLITAXEL AS 1ST LINE TREATMENT IN PATIENTS WITH ADVANCED LCNEC - MONDAY, DECEMBER 5, 2016

P1.07-004 UPDATED ANALYSIS OF PHASE II STUDY OF HA-IRINOTECAN, A CD44-TARGETING FORMULATION OF HYALURONIC ACID AND IRINOTECAN, IN SMALL CELL LUNG CANCER

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Background: Preclinical studies in small cell lung cancer (SCLC) have shown that hyaluronic acid (HA) can be effectively used to deliver irinotecan and selectively decrease CD44 expressing stem-like cell tumour cells. The current “proof of principle” study was aimed to replicate these findings by investigating the potential efficacy on clinical outcome according to CD44 expression. Final efficacy and bio-marker data on the study is presented. Methods: Patients with ESCLC, having measurable disease, suitable for safe biopsy and able to give informed consent were screened for this study. First 5 patients were treated with HA-irinotecan (150mg/m²) and carboplatin (AUC 5), every 3 weeks to evaluate safety data. Subsequent patients were stratified as first line or second line. All second line patients receive open label HA-irinotecan, while first line patients are randomized to receive either HA-irinotecan/ carboplatin or irinotecan/carboplatin. The response was measured by CT/PET at baseline, after 1 cycle and every 2 cycles subsequently. Baseline tumour samples were stained for CD44v6 (standard) and CD44v6 (variant 6). Blood samples for circulating tumour cells (CTCs) were also obtained at the baseline and before each treatment cycle till progression of disease. Results: Forty (40) patients, median age 66 (range 39-83) were enrolled on this study. Seven (7) patients either died or progressed before the first evaluation scan. Of the 29 evaluable patients, the overall response rate was 50%, with 6 (12%) complete and 13 (38%) partial responses. Four patients (12%) achieved stable disease while 7 patients (20%) progressed during the treatment. There was no PFS difference in the two first line treatment arms (median 28 weeks in experimental vs 42 week in standard arm) (P = 0.892 HR=0.93, 95% CI 0.36-2.04). Median PFS was 14.6 weeks in the second line cohort. The toxicity profile was similar to standard irinotecan, with the incidence of grade III/ IV diarrhoea seen in the experimental arm of 11% compared with 25% in the standard arm. Biomarker data was available in case of 24 patients, which suggested that there was no difference in response rates or survival according to baseline CD44v6 or CD44v6 expression. A possible correlation between the number of CTCs and tumour response and relapse was noticed. Conclusion: HA-irinotecan is well tolerated and has shown activity in the treatment of extensive stage small cell lung cancer. However, no improvement in efficacy was seen in CD44v6 or CD44v6 SCLC treated with HA-irinotecan. Further strategies to combine HA with other chemotherapeutic agents may be warranted.

Keywords: Hyaluronic acid, small cell lung cancer, CD44, irinotecan
Surgery, Aichi Cancer Center Hospital, Nagoya/Japan, flanks of NOD-SCID mice; treatments were initiated when tumors had reached 1 cm in diameter. Here, we evaluate the anti-tumor activity of topotecan, a TOP1 inhibitor, in a xenograft model of SCLC. Topotecan, a TOP1 inhibitor, is currently a standard of care for second-line treatment of small cell lung cancer (SCLC). TOP1 inhibitors are hypothesized to enable superior anti-tumor activity compared to traditional chemotherapy agents. Topotecan, delivered as a free base, was administered at a dose of 10 mg/kg/day, q2w. Topotecan was selected in preclinical studies due to its high tumor selectivity, low liver toxicity, and anti-tumor activity in both xenograft models of SCLC at clinically relevant dose levels, and resulted in complete or partial responses after 4 cycles in NCI-H1048 or DMS-53 models, respectively, compared with topotecan which had limited tumor growth control. Conclusion: This study demonstrated that topotecan is more active than topotecan at clinically relevant dose levels in SCLC preclinical models, and thus further support the clinical development of topotecan in patients with SCLC that have progressed on prior platinum-based therapy.

Keywords: small cell lung cancer treatment, irinotecan liposome, MM-398, topoisomerase I inhibitor

P1.07-008 LOMUSTINE ENDOXAN VP16 AS SECOND OR FURTHER LINE FOR RECURRENT OR PROGRESSIVE BRAIN METASTASES FROM SCLC

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Background: Up to fifty percent of patients with small-cell lung cancer (SCLC) will experience brain metastases (BM) during the whole course of their disease. The oral regimen Lomustine Cyclophosphamide Etoposide (LCE) has been tested in SCLC as second line treatment and was shown to be efficacious in the intravenous regimen Cyclophosphamide Adriamycin Vincristine (Gervais R et al. Clin Lung Cancer 2015;16:1005-5). This retrospective study evaluates the cerebral response rate (CRR) of this oral chemotherapy on brain metastases (BM) from SCLC relapsing after platinum-based chemotherapy. Methods: Patients with disease progression after one or more prior chemotherapy regimens for SCLC were included if they had at least one measurable BM according to RECIST 1.1, with PS 2. Patients with symptomatic BM were eligible. They were excluded if they had received previous whole brain irradiation before LCE or were receiving concomitant brain irradiation. Patients received the chemotherapy according to the following dosages: Lomustine 100 mg/m²/day, Etoposide 75 mg/m²/day, for 6 to 14 days, every 28 days, until progression or major toxicity. Primary prophylactic granulocyte colony-stimulating factor was recommended. The primary objective was the cerebral response rate (CRR) using RECIST 1.1. Secondary objectives included the extra-cerebral response rate, the overall survival and the safety. Results: From 2008 to 2014 in Baclesse comprehensive cancer center, 24 patients fulfilled the inclusion criteria. The median age was 57 years (interquartile range [IR] 51–65.5). CCR was 50% while ECRR was 26% (NS, p=0.135). Interestingly, 8 of the 9 patients with neurological symptoms had symptomatic improvement. Previous treatment (chemotherapy and/or radiotherapy) for BM did not appear to have any effect on CRR (p=1.000). The hematologic toxicities were the most common side effects with neutropenia (grade 3/4 = 26%) and thrombocytopenia (grade 3/4 = 31%). Median overall survival was 6.3 months. Conclusion: In our study, Lomustine Cyclophosphamide Etoposide has a high activity on BM from SCLC, with a comparable extra cerebral response rate than others regimen currently used in second line setting. It has a manageable toxicity profile and the oral route allows patients with a short expectancy of life to benefit from a home-delivered treatment. We suggest that this combination should be tested in a prospective study.

Keywords: brain metastases, small cell lung cancer, Second Line, Lomustine

P1.07-009 OUTCOMES OF PATIENTS WITH RELAPSED SMALL-CELL LUNG CANCER TREATED WITH PACLITAXEL PLUS GEMCITABINE. 10 YEAR-ANALYSIS

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Background: Although small cell lung cancer (SCLC) is generally considered a systemic disease even in patients with limited stage (LS). Selected recurrent LS-SCLC patients after chemoradiation treatment have been reported long survival with receiving salvage surgery. Purpose of this study was to find candidates for salvage surgery. Methods: We retrospectively reviewed the charts of 43 consecutive patients who were treated with chemoradiotherapy for LS-SCLC at our hospital from January 2011 to December 2015 to search for the patients with locoregional progression without mediastinal lymph node involvement. Results: Of the 43 patients, the median age was 69 (38-83), 91% were male and all of them had ECOG PS 0 or 1. Clinical stage: IIA (12%), IIB (2%), IIIA (8%), IIIB (5%). 35 (81%) received hyperfractionated RT (46Gy/30fr/3w). Objective response rate was 95%. One patient died of pneumonia. The median survival time was 1584 days and the median progression free survival was 280 days. 33 (77%) demonstrated disease progression. The first progression site was distant (include pulmonary metastasis and malignant pleural effusion) in 17, locoregional in 11, lymph node metastasis out of the radiation field in 2 and both distant and locoregional in 3. In the locoregional progression patients, 6 developed mediastinal lymph node progression in their clinical courses. Finally, 5 in 33 progressive patients had locoregional progression without mediastinal lymph node progression, and were thought possible candidates for salvage surgery. Conclusion: Most of the patients experienced distant metastasis and/or mediastinal lymph node progression. About 15% of patients who presented with apparently localized disease at the primary pulmonary site after chemoradiation might become possible candidates for salvage surgery.
Background: We conducted a retrospective study to investigate the outcome and prognostic factors of patients with relapsed SCLC who receive second or third line chemotherapy with paclitaxel plus gemcitabine, a regimen that is used in our institution since a phase II trial in 2001. We reviewed the medical records of patients with SCLC who received paclitaxel plus gemcitabine (PG) at any moment of the disease. Results: The median age of the cohort was 58 years (43–81 years). There were 69 males (83.2%) and 14 females (16.8%). 72 patients (86.7%) had a previous history of smoking. ECOG PS at registration was 0 in 3 (3.6%), 1 in 70 (84.3%), and 2 in 10 (12.1%) patients. Fifty patients (60.2%) had extensive disease at baseline diagnosis, and the remaining 33 (38.8%) had limited disease. All patients were exposed previously to etoposide and platinum. The platinum used was cisplatin in 52 patients (60.3%) and carboplatin in 30 patients (37.8%). Previous radiation at local tumor site was received by 38 patients (62.8%). The response was evaluated in 78 patients. The response post 2 months of PG was complete response in 2 patients (2.5%), partial response in 29 (37.1%), stable disease in 24 (30.7%), and progressive disease in 23 patients (30.6%). The median number of cycles of PG received was 8 (2–28 cycles). Toxicity related cessation of treatment was required in 12 patients (14.4%). The reason for stoppage was Grade 3–4 toxicities in 8 patients (9.6%) and deterioration in PS in 4 patients (4.8%). The median PFS was 148 days (95% CI: 30–173.5 days) while the median OS was 172 days (95% CI: 60–485 days). Conclusion: Paclitaxel plus gemcitabine is a well tolerated regimen in relapsed SCLC in the schedule we usually use (every 2 weeks). Unless this study is retrospective, we believe that this combination can be used nowadays in these patients, if there is no clinical trial available.

Keywords: SCLC, chemotherapy, second line

P01.07-011 EXTENSIVE-STAGE SMALL CELL LUNG CANCER IN A 13-YEAR-OLD MALE PATIENT TREATED WITH BEVACIZUMAB FOLLOWED BY HIGH-DOSE CHEMOTHERAPY

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Background: Small cell lung cancer (SCLC) is exceedingly rare in children. Methods: We herein report a pediatric case of extensive-stage SCLC in a patient who was treated with intensive chemotherapy and high-dose chemotherapy (HDC). Results: A 13-year-old male patient was admitted to our department with a three-month history of cough. Thoracic CT and MRI showed two large masses, one was a 5.8 × 4.3 × 3.9 cm primary tumor that was located close to the right middle lobe bronchus; the other was a subcarinal lymph node. Systemic PET-CT revealed multiple bone metastases. A serological analysis revealed high levels of pro-GRP (4,075 pg/mL [normal, ≤81 pg/mL]) and NSE (52.3 ng/mL [normal, ≤16.3 ng/mL]). The patient’s plasma level of VEGF was 259 pg/mL (normal, ≤15 pg/mL). We diagnosed the patient with SCLC based on the results of the histopathological examination of endoscopically-obtained biopsy specimens that were obtained from part of the tumor that was partially exposed on the bronchial wall. Treatment was initiated with cisplatin and irinotecan (PI). After four courses of PI therapy followed by two courses of PI plus etoposide (PIE) therapy, there was a reduction in the tumor volume and a remarkable decrease in the patient’s biomarker levels. Therefore, we administered three courses of chemotherapy consisting of bevacizumab and cyclophosphamide, vincristine, doxorubicin, and etoposide (BEP). The patient’s platelet count reached 131 × 10^4/µL and the patient’s platelet count reached 131 × 10^4/µL, and he was given high-dose chemotherapy with autologous peripheral blood stem cell rescue and prophylactic cranial irradiation were performed. Early recurrence appeared one month after the completion of the series of initial treatments. He died ten months after the relapse. Conclusion: The long-term prognosis of adult SCLC patients is generally poor, even if desirable initial treatment responses are obtained. In order to improve their prognosis, new trials with other anti-cancer agents should be performed. Bevacizumab, an anti-VEGF monoclonal antibody that is effective against non-SCLC, is an intriguing candidate molecular target drug that should be evaluated for SCLC. Because the value of VEGF in the present patient’s plasma was high, we were of the opinion that the administration of bevacizumab after effective chemotherapy with PI and PIE might have represented an intensive treatment that had the potential to improve his prognosis. Because intensive chemotherapy has been observed to be highly tolerable in adolescence and young adults, we expected HDC to have a greater effect on the patient’s disease. However, the intensive chemotherapy strategy had no impact on the patient’s disease and the results were similar to those observed in elderly patients with extensive-stage SCLC.

Keywords: SCLC, high-dose chemotherapy, bevacizumab, adolescence and young adult

P01.07-012 EFFICACY OF IMMUNE CHECKPOINT INHIBITORS IN LARGE CELL NEUROENDOCRINE LUNG CANCER: RESULTS FROM A FRENCH RETROSPECTIVE COHORT

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Background: Nivolumab and pembrolizumab, two programmed death (PD)-1 immune-checkpoint–inhibitor antibodies, demonstrated superior versus standard chemotherapy in second- third line in both squamous and non-squamous lung cancer. Large cell neuroendocrine lung cancer (LCNEC) is a rare tumour often treated as a small cell lung cancer, but there is not a standard of care after a first line progression. Aim of the study was to assess clinical efficacy of PD-1 inhibitors in these patients. Methods: We retrospectively reviewed all consecutive LCNEC stage IIIB- IV patients treated with nivolumab or pembrolizumab after platinum-based first line therapy between July 2014 and November 2015 in six French centres. Patients were followed until June 2016. The drugs were given in an early access program or a clinical trial. Results: The analysis included 10 patients with advanced stage disease. Eight patients (80%) had a stage IV disease with a median age of 59 [interquartile range (IQR) 55–62] years. The majority were males (n=9, 90%), with good performance status (0;1;9/90%) and 50% were treated in third line

Keywords: creatinine clearance, small cell lung cancer, survival

P01.07-013 IMPACT OF CREATININE CLEARANCE ON SURVIVAL PARAMETERS IN SMALL CELL LUNG CANCER TREATED WITH CISPLATIN-BASED CHEMOTHERAPY REGIMEN

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Poster Session 1: P01.07: SCLC/NEUROENDOCRINE TUMORS
Drug Treatment Alone and in Combination with Radiotherapy – Monday, December 5, 2016
Conclusion: although admission of oral topotecan is well tolerated it is related the most serious was grade 3 or 4 diarrhea that occurred in 5 patients (7.8%).

Criteria. Anemia grade 3 or 4 occurred in 13 patients (20.3%). Grade 3 or 4 toxicities were assessed using the National Cancer Institute Common Toxicity Criteria. The majority of patient hospitalizations (11 patients, 16.9%) was due to adverse events related to topotecan administration. The majority of patient hospitalizations (11 patients, 16.9%) was due to febrile neutropenia. Other reasons for hospitalization were severe diarrhea in 4 patients (6.2%), pneumonia in 1 patient (1.5%) and severe electrolyte imbalance in 2 patients (3.1%). If admission to hospital 10 (28.9%) of them were after application of first chemotherapy cycle, 3 (16.7%) after second cycle and 4 (23.5%) after third cycle. Quantitative hematologic toxicities were assessed using the National Cancer Institute Common Toxicity Criteria. Anemia grade 3 or 4 occurred in 13 patients (20.3%). Grade 3 or 4 neutropenia occurred in 7 patients (10.9%). Grade 2 or 4 neutropenia occurred in 16 patients (25%). Of other, non-hematologic adverse effects the most serious was grade 3 or 4 diarrhea that occurred in 5 patients (7.8%).

Conclusion: admission of oral topotecan is well tolerated it is related to high rate of hospitalizations due to myelotoxicity and gastrointestinal toxicity during therapy.

Keywords: SCLC, topotecan, side effects

P1.07-015 STOMP: A UK NATIONAL CANCER RESEARCH NETWORK RANDOMISED, DOUBLE BLIND, MULTICENTRE PHASE II TRIAL OF OLAPARIB AS MAINTENANCE THERAPY IN SCLC

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Background: STOMP (IRCTN 73164486, CRUK/10/037, EudraCT 2010-021156-76) is a randomised, double-blind, placebo-controlled phase II trial to evaluate activity and safety of the PARP inhibitor olaparib (AstraZeneca) as maintenance treatment for patients with chemo-responsive small cell lung cancer (SCLC). Two schedules of olaparib oral tablets were investigated: 300mg twice daily (bd) or 200mg three times daily (tds). Methods: Eligible patients had pathologically confirmed SCLC with response to first line chemotherapy or chemo-radiotherapy. Patients were stratified by metastasis-status and prior radiotherapy use. Patients received either olaparib bd, tds, olaparib bd, placebo tds or placebo bd. Placebo arms were pooled for analysis. Primary outcome was progression-free survival (PFS). There is 80% power to detect a difference of 3 months in PFS from 4.8 months between treatments based on a one-sided 5% significance level. Key secondary outcomes were overall survival (OS), adverse events (AEs) and quality of life. Results: Between November 2013 and December 2015, 220 UK patients were randomised. Arms were well balanced for stratification factors of prior radiotherapy (98% Yes) and metastasis status (66% M) and age (median=64, range 42-89). Median follow-up for 31 event-free patients was 14 months (range 0–24). Median PFS was 2.6 (90% CI 1.8, 3.7) and 3.6 (90% CI 3.1, 6.0) and 3.6 (90% CI 3.1, 4.7) months in the placebo, olaparib bd and tds arms, respectively. There was no significant difference in PFS between olaparib and placebo for either the bd (Cox-Adjusted HR 0.87, 90% CI 0.80, 0.95) or the tds arm (0.89, 90% CI 0.87, 1.05, p=0.03). Median OS was 8.9 (90% CI 7.0, 11.9) and 9.3 (90% CI 7.6, 12.9) and 9.0 (90% CI 6.6, 11.8) months in the placebo, olaparib bd and tds arms, respectively. There was
no significant difference in OS between olaparib and placebo for either the bd (Cox-Adjusted HR 0.97, 90% CI 0.90 to 1.04; stratified logrank p=0.16) or tds arm (1.05; 90% CI0.89, 1.24; p=0.73). The most common AEs on olaparib were fatigue, nausea, anemia, vomiting and anorexia. 68 patients discontinued treatment citing AEs (17 placebo, 26 olaparib bd, 25 olaparib tds). Conclusion: There is no evidence that either the bd or tds regimen for olaparib improves PFS or OS in an unselected population. The AE profile for olaparib in SCLC is similar to that observed in other studies.

Keywords: maintenance, SCLC, PARP, olaparib

P1.07-016 TRENDS, PRACTICE PATTERNS AND UNDERUSE OF SURGERY IN THE TREATMENT OF EARLY STAGE SMALL CELL LUNG CANCER
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Background: Current National Comprehensive Cancer Network guidelines recommend pathologic mediastinal staging and surgical resection for all patients with clinically node negative T1 and T2 small cell lung cancer (SCLC), but the extent to which surgery is used for early stage SCLC is unknown. Our objective was to assess trends and practice patterns in the use of surgery for SCLC. Methods: Clinical stage T1 or T2 N0M0 SCLC cases were identified in the National Cancer Database (NCDB), 2004 – 2013. Demographics and clinical characteristics of patients undergoing resection were analyzed. Hierarchical logistic regression was used to identify individual and hospital-level predictors of receipt of surgical therapy. Trends in the rates of surgical resection for eligible patients were analyzed over the study period. Results: 9,740 patients were identified with a diagnosis of clinical T1 or T2 N0M0 SCLC. Of these, 2,210 underwent surgery (22.7%), with 1,421 (64.3%) of these patients undergoing lobectomy, 739 (33.4%) sublobar resections and 50 (2.3%) pneumonectomies. Medicaid patients were less likely to receive surgery (OR 0.65 95% CI 0.48 – 0.93, p=0.006), as were those with T2 tumors (OR 0.25 CI 0.22 – 0.29, p<0.0001). Academic facilities were more likely to resect eligible patients (OR 1.90 CI 1.45 – 2.49, p<0.0001). Between 2004 and 2013, rates of resection more than doubled from 9.1% to 21.7%. Overall, 68.7% of patients were not offered surgery despite having no identifiable contraindication. In patients not receiving surgery, only 7% underwent pathologic mediastinal staging.

Figure A. Reason for patients not undergoing or being offered surgery, shown by year of diagnosis. Contraindication to surgery includes advanced age or other medical comorbidities precluding resection.

Conclusion: Although rates of resection are increasing, surgery is rarely used nationally in the treatment of potentially eligible SCLC patients. About two thirds of potentially eligible patients fail to undergo potentially curative surgery. Further study is required to address the lack of concordance between guidelines and practice.

Keywords: small cell lung cancer, Health Services Research, quality improvement

P1.07-017 INDICATIONS FOR ADJUVANT MEDIASTINAL RADIATION IN SURGICALLY RESECTED SMALL CELL LUNG CANCER
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Background: Adjuvant mediastinal radiation (AMR) is an adjunctive therapy for patients with surgically resected small cell lung cancer (SCLC). However, little data guides its use. We sought to examine whether there was a survival benefit associated with AMR for resected SCLC patients and to define sub-populations who should be selected for AMR. Methods: Patients undergoing resection (lobectomy, pneumonectomy and sublobar resection) for SCLC were identified in the National Cancer Database, 2004 – 2013. Kaplan-Meier survival curves and Cox proportional hazards were used to evaluate the impact of receipt of AMR on survival. Hazard ratios were adjusted for patient comorbidity and demographic information, as well as tumor stage, grade, histology, margin status and receipt of adjuvant chemotherapy. Results: 3,113 patients were identified. Those receiving AMR were younger, more likely to have greater pathologic T- and N-stage, more likely to undergo sublobar resection and have a positive margin. Kaplan-Meier curves showed better median survival for patients with N1-3 disease who received AMR. After adjustment, Cox models showed lower risk of death for N1, N2/3 and sublobar resection with AMR (HR0.79 CI0.65 – 0.96, p<0.02; HR 0.60 CI0.48 – 0.75, p<0.0001). In the overall cohort, AMR was not associated with better survival in node-negative patients. AMR was, however, associated with improved survival for patients receiving sublobar resection (HR0.72 CI0.58 – 0.92, p=0.006).

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Conclusion: AMR has significant benefit for node-positive patients after resection for SCLC, especially those with pN2 or pN3. Patients undergoing sublobar resection may benefit from AMR.

Keywords: adjuvant mediastinal radiation, small cell lung cancer

P1.07-018 INCIDENCE OF BRAIN RECURRENCE AND SURVIVAL OUTCOMES IN HIGH-GRADE NEUROENDOCRINE CARCINOMAS OF THE LUNG: IMPLICATIONS FOR CLINICAL PRACTICE

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Background: Among patients with advanced high-grade neuroendocrine carcinoma (HGNEC) of the lung, the optimal therapeutic management is much less established for large cell neuroendocrine carcinomas (LCNECs) than for small cell lung cancers (SCLCs). We evaluated the survival outcomes and incidence of brain recurrence of advanced LCNECs, and compared them with those of a population of SCLCs matched by stage. Methods: Forty-eight unresected stage III HGNECs (16 LCNECs and 32 SCLCs) and 113 stage IV HGNECs (37 LCNECs and 76 SCLCs) were eligible for the analysis. The efficacy of platinum-etoposide chemotherapy with or without thoracic radiotherapy (TRT) and/or prophylactic cranial irradiation (PCI) was investigated. Results: Overall response was significantly lower for LCNECs compared with SCLCs for both stage III (43.8% vs 90.6% respectively, P=0.004) and stage IV (43.3% vs 64.5%, respectively, P=0.04). Similarly, an inferior outcome was observed in terms of progression-free survival (PFS), and overall survival (OS) for LCNECs compared with SCLCs, which, however, reached significance only for stage III disease (median: 5.6 vs 8.9 months, P=0.06 and 10.4 vs 17.6 months, P=0.03 for PFS and OS, respectively) (Figure 1). Histologic subtype (LCNEC vs SCLC) was an independent prognosticator in multivariate analysis. In the lack of PCI, LCNECs showed a high cumulative incidence of brain metastases, as 58% and 48% of still living stage III and IV patients, respectively, developed brain metastases at 18 mo.

Conclusion: Patients with advanced LCNECs are at high risk for brain recurrence. Unresected stage III LCNECs treated with platinum-etoposide with or without TRT bear a dismal prognosis, when compared indirectly with SCLC counterparts. Randomized trials should evaluate whether PCI could improve survival of advanced LCNECs.

Keywords: small cell lung cancer, prophylactic cranial irradiation, Neuroendocrine tumors, Large Cell Neuroendocrine tumours

P1.07-019 LARGE CELL NEUROENDOCRINE CARCINOMA OF THE LUNG: PROGNOSTIC FACTORS OF SURVIVAL AND RECURRENCE AFTER RO SURGICAL RESECTION

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Background: Large cell neuroendocrine carcinomas (LCNEC) represent approximately 3% of all lung cancers. Due to this rarity, little knowledge exists about their outcome, prognosis or optimal treatment strategy. The objective of this study is to evaluate the outcomes of patients undergoing lung resection for LCNEC to identify the factors affecting survival and recurrence to help refine the optimal treatment strategy. Methods: We retrospectively reviewed 116 patients who underwent lung resection at 8 centers between 2000-2015. We excluded 18 patients: pNX(3), stage IV(5), R1-2(10). Univariate and multivariate analysis were performed to identify factors influencing disease-specific survival, overall survival and recurrence. The variables included age, gender, smoking habit, previous malignancy, ECOG performance status, symptoms at diagnosis, extent of resection, extent of lymphadenectomy, tumor location, tumor size, pt, pleura invasion, n, pStage and neo/adjuvant treatments. Kaplan-Meier, Cox regression and ROC curve were used. Results: A total of 98 patients (M/F=60/38) were analyzed with a median age of 66 years (IQR=58-72). Prior to resection, T1(11%) received...
involvement and non-radical surgery were the main elements able to affect and associated with considerable long-term survival. Mediastinal nodal SCLCs was 30.3 (95% CI: 7.03-36.9), while it was 14.7 (95% CI: 12-NA) months disease according to surgical resection. Median OS of surgically resected patients was 65.7 (95% CI: 44.5-108) months. To confirm our results, we compared outcome of patients with pN2 margins were found positive in 8 (13%) cases. Median OS for pN0-1 patients was 62.3 (95% CI: 32.4-82.1) and 12.8 (95% CI: 6.57-47.27) months, significant correlation between necrosis and mitosis (p 0.00002), and pN2 and expression were analyzed. Results: Median follow-up was 42 months. Clinical, radiological and pathological data were reviewed and related with outcome. Mitotic count, necrosis, TPS, Bcl-2 and PD-L1 immunohistochemical expression were evaluated. Among resected patients, 46 (75%) were male and median age was 68 (5% CI: 69-83.4) years. Seven patients (11%) underwent pneumonectomy, 43 (71%) received chemotherapy before (20%) or after (25%) surgery. Adjuvant radiotherapy was administered in 15 (31%) cases. Pathological review of resected SCLCs was performed. Median mitotic count was 10/10 hpf and extensive necrosis was found in 80% of samples. TPS (30%), Bcl-2 (H-index >150) and PD-L1 (5%) expression was reported in 58%, 58% and 62% of samples respectively. None of these factors significantly affected survival. A significant correlation between necrosis and mitosis (p 0.00002), and pN2 and Bcl-2 (p 0.03) was found. Median overall survival (OS) and disease-free survival (RFS) were 62.3 (95% CI: 32.4-82.1) and 12.8 (95% CI: 6.57-47.27) months, respectively. Mortality of surgery was 0%, morbidity was 23%. Surgical margins were found positive in 8 (13%) cases. Median OS for pNO-P1 patients was 65.7 (95% CI: 44.4-570) months versus 30.3 (95% CI: 12-NA) months for patients with pN2 disease (p 0.04). Multivariate analysis confirmed pN2 stage (p 0.04) and surgical margins (p 0.03) as significant prognostic factors. Among non-rectected patients, the median age was 69.4 (95% CI: 54.7-84) years. Median OS and RFS were 13.4 (95% CI: 7.26-9) and 7 (95% CI: 5.9-19) months. To confirm our results, we compared outcome of patients with pN2 disease according to surgical resection. Median OS of surgically resected SCLCs was 30.3 (95% CI: 7.03-36.9), while it was 14.7 (95% CI: 12-NA) months among patients treated with chemoradiotherapy, but the comparison was not statistically significant. Conclusion: Radical-intent surgery was feasible and associated with long-term survival. Mediastinal nodal involvement and non-radical surgery were the main elements to affect OS. The expression of PD-L1 was not prognostic in stage-III SCLCs. Further prospective studies are warranted to optimize multimodal approach and selection of patients.

Keywords: large cell neuroendocrine carcinoma, prognostic factors of survival, lung surgery, prognostic factors of recurrence


P1.07-021 IMPACT ON SURVIVAL OF HIGH DOSE CONSOLIDATIVE THORACIC RADIOTHERAPY IN EXTENSIVE STAGE SMALL CELL LUNG CANCER
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Background: Consolidative thoracic radiotherapy for metastatic small cell lung cancer patients who have responded to chemotherapy is controversial. Some publications suggest improved local control which could induce survival. Slotman et al. have recently published a randomized study that showed that thoracic radiotherapy improves long term survival for patients with extensive stage small cell lung cancer (ES-SCLC) who have responded to chemotherapy. Slotman also demonstrated in 2007 that prophylactic cranial irradiation in metastatic small-cell lung cancer with response to initial chemotherapy, reduces the incidence of symptomatic brain metastases and prolongs disease-free and overall survival. Methods: In our Radiation Oncology Department we have reviewed those patients with ES-SCLC (disseminated disease excluding brain metastases) who have achieved a subjective response after chemotherapy, received prophylactic cranial irradiation and, after that, some of them treated with consolidative thoracic radiotherapy (CRT). Between 1995 and 2015 we have treated 68 patients, 59 men and 9 women (median age 63 years, range 42-79), with the characteristics mentioned above. Prophylactic cranial irradiation was administered at median doses of 24 Gy (range 24-36.6y). Thoracic radiotherapy consolidation was delivered to 23 patients (33.8 %), with a median total dose of 64 Gy (range 20-54 Gy). We compared this group with the 45 patients (66.2 %) who did not receive CRT. Results: Among those patients treated with CRT, 17 patients (37.4 %) had residual disease after chemotherapy, 4 patients (7.9 %) had chest progression and 2 patients (3.8 %) achieved complete response. No grade 3 toxicity has been reported. Median overall survival (OS) is 18 months in patients who received CRT, compared to 10 months in those patients who have not CRT. OS after one year was 78.3 % in the group of patients with CRT and 13.3 % when CRT was not performed. OS after two years was 34.8 % with CRT and 6.9 % without CRT. Conclusion: We have found a benefit (p = 0.002) in the group of patients who received CRT, compared with patients who did not, obtaining significant differences in median survival and overall survival, taking into account that a bias selection could have affected the results. In comparison with Slotman study, we have found an improved survival with higher doses of CRT, without additional severe toxicity.

Keywords: thoracic radiotherapy, Consolidative radiotherapy, extensive small cell lung cancer


P1.07-022 THE ROLE OF SURGERY IN COMBINATION TREATMENT OF PATIENTS WITH SMALL CELL LUNG CANCER
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Background: Small cell lung cancer (SCLC) as the most aggressive tumor deserves a special attention. The aim of this research was to define the place of surgery of patients with SCLC in order to improve the procedures of treatment. Methods: Clinical material for research consists of 46 patients in stage IA-IIIA with SCLC, which were radically operated in Ugra (region Russia) between 1999 and 2013. Among patients predominates males 38 (82.6%), versus females – eight (17.4%). Results: All patients underwent radical operations R0. All residual tumors were resected (lobectomy, bilobarctomy, and lobectomy). By 32 patients (69,6%) systemic nodal dissection (SND) was carried out, by 5 (10,9%) - mediastinal lymph node sampling (MNS) and by 9 patients mediastinal node dissection was not carried out. By SCLC combination treatment was used more often – 32 (69,6%). By that only in 8 cases additional adjuvant of thoracic radiotherapy was used.
In 14 cases only surgical resection was used (30.4%). 5-year overall survival (OS) rate was 47.1%. Median survival rate was 58 months. Five-year OS rate by surgery combined with adjuvant chemotherapy was 52.1%, as compared to only surgical treatment – 35.6%. At I stage satisfactory results were achieved: 5-year OS rate was 69% (p<0.05), – that corresponds with results of treatment of patients with non-small cell lung cancer with similar stage of process. Median survival rate was not achieved. At II stage 5-year OS rate was 31%. Median survival rate was 46 months. At III stage unsatisfactory results were obtained: 5-year OS rate was 21%. Median survival rate was only 11 months. Conclusion: SCLC at I and II stages is the indication to radical treatment, mandatory including surgical resection with SND and adjuvant chemotherapy. The main method of treatment at III stage is chemotherapy or chemoradiotherapy.

POSTER SESSION 1 - P1.07: SCLC/NEUROENDOCRINE TUMORS
Molecular Changes – MONDAY, DECEMBER 5, 2016

P1.07-023 NGS MAY DISCRIMINATE EXTREME LONG-TERM VERSUS SHORT-TERM SURVIVAL IN PATIENTS WITH STAGE IV SMALL-CELL LUNG CANCER (SCLC)
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Background: Molecular underpinnings that may prognosticate survival and could increase our understanding of tumor progression are far less understood processes in highly aggressive malignancies such as SCLC. We aimed to describe the clinicopathological characteristics and biomarker profiling of short versus long-term SCLC survivors using the latest, most clinically actionable genomic and immunohistochemical (IHC) alterations.

Methods: Consecutive 876 metastatic SCLC patients receiving standard of care therapy were evaluated between 2000 and 2013 at the National Kanoriy Institute of Pulmonology. Long-term (LT) (overall survival (OS) > 24 months) and short-term (ST) survivors (OS range 2-9 weeks) with histologically confirmed stage IV SCLC were included in this retrospective analysis. DNA and RNA were isolated from FFPE tissues. A comprehensive next-generation sequencing test (NGS) was performed to analyze gene mutations, copy number variations (CNV), mRNA expression, and protein expression by IHC (PCDx, Paradigm). Multiplex sequencing analysis had coverage >5,000x.

We then evaluated the associations among these various biomarkers and clinicopathological characteristics. Results: Four LT and 11 ST were identified for NGS. There were five mutually exclusive gene mutations, and clinicopathological characteristics. Results: Four LT and 11 ST were identified for NGS. There were five mutually exclusive gene mutations,
and lower epithelial molecule β-catenin, while suppression of Etk/BMX was opposite. Knockdown of Zeb-2 and Twist inhibited the chemoresistance of cells. Conclusion: Our study revealed that miR-495 promoted chemoresistance of SCLC through epigenetic mesenchymal transition via Etk/BMX. Milk-495 re-expression or Etk/BMX depletion is a promising strategy for interfering with chemoresistance in SCLC.

Keywords: Etk/BMX, small cell lung cancer, chemoresistance, miR-495

POSTER SESSION I - P1.07-02 ACTIVIN A IS ASSOCIATED WITH POOR PROGNOSIS AND PROMOTES METASTATIC GROWTH IN SMALL CELL LUNG CANCER

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Background: Small cell lung cancer (SCLC) is a devastating malignancy characterized by resistance to therapy and poor clinical outcome. Therefore, identification of novel therapeutic strategies and non-invasive biomarkers that facilitate early detection and predict prognosis is urgently needed. Expression of the growth factor activin A (ActA), a member of the TGF beta superfamily, is deregulated in a number of malignancies. However, to date there is no data on the role of ActA in SCLC. Methods: In a cohort of SCLC patients (n=39) and in sex- and age-matched controls (n=66), plasma levels of ActA were measured by ELISA. The diagnostic value of plasma ActA was evaluated by ROC curve analysis. The mRNA and protein expression levels of ActA were analyzed in SCLC cell lines by qRT-PCR and by ELISA, respectively, and one of the cell lines with low baseline ActA expression was transfected with ActA and a control vector. The effect of ActA overexpression on the in vivo growth of SCLC was investigated in an orthotopic xenograft model. Results: Increased plasma ActA levels were found in patients with SCLC (vs. controls) and ActA levels were elevated in a TNM stage-dependent manner. Moreover, high ActA levels were associated with significantly shorter overall survival and multivariate analysis revealed that plasma ActA concentration is an independent negative prognostic factor in this patient cohort. With an area under the curve of 0.81 (95% CI: 0.74-0.88), circulating ActA was identified as a useful biomarker for the diagnosis of SCLC. Expression of ActA in SCLC cell lines was detected in vitro. Furthermore, ActA overexpression increased the metastatic capacity of SCLC cells in our xenograft model. Conclusion: Our findings suggest that the measurement of circulating ActA can support the diagnosis and staging of SCLC and, moreover, that it can help to predict the clinical outcome. We also conclude that ActA has a role in the aggressive behavior of this tumor type and that its potential therapeutic relevance needs to be further investigated.

Keywords: small cell lung cancer, activin A, prognosis, metastasis

POSTER SESSION I - P1.07-02 DUAL ROLE OF THE FOCAL ADHESION KINASE IN SMALL-CELL LUNG CANCER

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Background: Small-cell lung cancer (SCLC) is a devastating illness with five-year overall survival as low as 5%. The molecular steps leading to SCLC development and progression are still poorly understood and this has translated into the absence of targeted therapies. Focal Adhesion Kinase (FAK) is a non-receptor tyrosine kinase which regulates integrin and growth factor signaling pathways involved in cell proliferation, survival, migration, and invasion. FAK is overexpressed and/or activated in many cancers, including SCLC. We hypothesized that FAK overexpression/activation in SCLC contributes to its aggressive behavior and that FAK may represent a therapeutic target in SCLC. Methods: Two SCLC cell lines growing in suspension (NCI-H28, NCI-H146), and adherent SCLC cell lines (NCI-H115, NCI-H446) were treated with PF-228. NCI-H446 and H82 cells were stably transfected with FAK shRNA and/or FRNK using lentivirus vector. Cell proliferation was evaluated by WST-1 assay; cell cycle by flow cytometry with propidium iodide and bromodeoxyuridine; apoptosis by caspase 3 staining in flow cytometry and by cleaved PARPp85 Western blotting (WB); motility by wound healing assay; and invasion by Boyden chambers. FAK expression/ activity was evaluated by WB. Results: While PF-228 did not modify total FAK expression, it decreased FAK phosphorylation (Y397). Inhibition of FAK activity by PF-228 decreased cell proliferation, DNA synthesis, induced cell cycle arrest in G2/M phases, and increased apoptosis in dose-dependently. PF-228 also decreased motility in the adherent H196-H446 cells. To confirm the specificity of the antitumoral effects of PF-228, we stably transfected SCLC cells with FAK shRNA and FRNK and then analyzed the phenotypic changes induced by these approaches. Knockdown of total FAK protein by knockdown of FAK shRNA inhibited FAK activity, but did not have any effect on cell proliferation, DNA synthesis, and cell cycle. However, reintroduction of FRNK in cells stably transfected with FAK shRNA inhibited cell proliferation and DNA synthesis. Expression of FRNK decreased cell proliferation and DNA synthesis in SCLC cells. Conclusion: Inhibition of FAK activity by PF-228 in SCLC cell lines demonstrates that FAK activity is required for cell proliferation, cycle progression, survival, and motility, suggesting that FAK inhibition may represent a suitable therapeutic target for SCLC. Inhibition of FAK by a generic approach suggests that FAK has a dual role in SCLC biology, namely (i) a pro-tumoral effect related to the kinase domain, which induces downstream signals (ii) an anti-tumoral effect mediated by the non-kinase C-terminal domain (FRNK domain), which keeps inactive other pro-tumoral effectors.

Keywords: Targeted therapy, FAK, SCLC

POSTER SESSION I - P1.07-02 13-GENE SIGNATURE OF EMT REVEALS IMPACT ON INVASION AND METASTASIS OF NEUROENDOCRINE CARCINOMAS OF THE LUNG: A PRELIMINARY STUDY

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Background: Metastasis are responsible for the death of 90% of patients with lung cancer, indicating the need to know the multiple signaling pathways involved. Neuroendocrine lung carcinomas (NELC) encompass a wide spectrum of tumors, from the low-grade typical carcinoid (TC) and atypical carcinoid (AC), to the high-grade large cell neuroendocrine carcinoma (LCNEC) and the small cell lung carcinoma (SCLC). Low-grade NELC are indolent, while high-grade NELC invade and metastasize rapidly. Biomarkers of NELC aggressiveness remain to be determined. Epithelial to mesenchymal transition (EMT) genes profile emerge promise as indicator of invasion and metastasis. Our aim was to evaluate: (1) EMT gene expression in NELC, (2) its relationship with the histologic subtypes and (3) its impact on behavior of the tumors. Methods: Patients with SCLC (n = 10), LCNEC (n=5), AC (n=2) and TC (n=7) were included, EMT gene expression was quantified with a quantitative real-time (RT)-PCR carried out on StepOnePlus™ Real-Time PCR System (Applied Biosystems), with RT2 Profiler PCR Array System for the Qiagen, Dusseldorf, Germany. Associations of the gene expression profiling and clinicalopathological features, as well as prognostic factors were evaluated. Results: A 13-gene signature (AHNAK, COL3A1, DSP, ILIRN, MSN, PDGFRB, SNAI1, SNAI3, TCF3, TGF1, TGFJ2, TGFJ3 and VIM) that was related to EMT was up-regulated in tumor-tissue from all NELC patients, mainly in those with high-grade NELC. An increased expression of DSP, TCF3 and TGF1 in patients with high-grade NELC was found in SCLC compared to AC, TC and LCNEC, and associated with lymph nodes metastasis with statistical significance respectively for DSP (p=0.03 and 0.02), TCF3 (p=0.02) and marginal significance for TCF3 and TGFJ3 (p=0.08 and p=0.08). TCF3 was also associated with tobacco history (p=0.04). A significant correlation was found between ILIRN and VIM (r=0.3), chromosome 3 and TGFJ2 (p=0.04), synaptophysin and TGFJ1 and TGFJ2 respectively (p=0.04 and p=0.02). Conclusion: The EMT analysis identified genes involved in cell proliferation, motility, invasion and metastasis of NELC. We further inferred DSP, TCF3 and TGFJ3 as target against lung cancer metastasis and invasion, thus arising as promising therapeutic agent.

Keywords: Gene signature, EMT, Neuroendocrine carcinomas, lung cancer
Background: Small cell lung cancer (SCLC) accounts for 15% of all lung cancer cases. SCLC is notoriously difficult to treat with high relapse rate and the current standard treatment remains chemotherapy. Arginine is an important amino acid in normal human cells that can be replenished through urea cycle, but some tumors are arginine-auxotrophic due to deficient argininosuccinate synthetase (ASS1) and/or ornithine transcarbamylase (OTC). BCT-100 is a pegylated arginase, which converts arginine to citrulline, has demonstrated antitumor activity in human melanoma, hepatocellular carcinoma and acute myeloid leukemia. We aim to determine the in vitro effects of BCT-100 in SCLC Methods: A panel of 7 SCLC cell lines was obtained from ATCC. Cell viability was detected by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay and protein expression by Western blot. Knockdown of OTC was performed using siRNA. Flow cytometry was applied to detect mitochondrial membrane depolarization (MMD). Results: The IC50 values of BCT-100 in H69, DMS59, H187, H205, HS82, HB41 and SW1271 cells were 462.9±12.2, >1000, 24.9±6.4, 8.6±0.8, 10.1±0.7, >1000 and 49.2±7.4 μM/mL respectively. Overexpression of ASS1 in H69 and DMS59 cells, and OTC in HB41 cells were associated with resistance to BCT-100. Knocking down of OTC increased sensitivity of BCT-100 in HB41 cells partially via apoptosis. HS62 cells (BCT-100-sensitive) was selected for mechanistic study. MMD was observed in BCT-100 treatment accompanied by cytochrome c and SMAC release from mitochondria to cytosol. N-acetylcysteine (NAC) could significantly reverse apoptosis induced by BCT-100. Besides, cyclin A2, cyclin B1 and CDK7 were downregulated in a time-dependent manner. The protein expression of p-AKT and p-mTOR was increased after exposure while RAS/RAF/ERK cell signaling pathway was inhibited with BCT-100 treatment. Conclusion: SCLC cell lines with low ASS1 and OTC expression were sensitive to arginine depletion with BCT-100, mediated through oxidative stress, cell cycle arrest and apoptotic pathway.

Keywords: small cell lung cancer, apoptosis, Pegylated arginase BCT-100, oxidative stress

P1.07-032 MOST COMMON GENOMIC ALTERATIONS IN SCLC

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Background: Lung cancer is the leading cause of cancer death in US. The American Cancer Society’s estimates for lung cancer in the United States for 2016 are: approx 224,390 new cases of lung cancer and approx 158,080 deaths. Approximately 10.15% of lung cancers are classified as small cell (SCLC). These cancers portend a poor prognosis. Genomic sequencing of non-small cell lung cancer led to developing of new therapeutic modalities, i.e. targeted therapy.
with superior results to conventional cytotoxic chemotherapy. At this time, there is no approved targeted therapy for SCLC. In order to develop targeted therapies we need to identify and characterize molecular targets (alterations). This study aims to report our experience with genomic sequencing of SCLC. Methods: We performed a retrospective analysis of a dataset of 54 cases of SCLC, who underwent genomic sequencing. Patients were treated at 5 tertiary referral centers, between October 2012 and June 2016. The recorded data included: age at diagnosis, date of the genomic sequencing, genomic alteration (affected genes and the type of molecular alteration identified). For genomic profiling we used a platform commercially available (FoundationOne). Results: We obtained 54 samples from 54 patients. Age range is 42 to 75 years, mean 60 and median 61 years old. All cases had a histologic diagnosis of SCLC. The genomic analysis found 88 affected genes with 230 alterations. The most common affected genes: Tp53 alteration, 45 cases (83%) and Rb1 33 cases (61%). There were an average of 4.3 mutations per patient, with a median of 4 mutations per patient, with a minimum of 0 and a maximum of 13.

Conclusion: Sustained investigations and sequencing of larger numbers of SCLC are aiming to identify potential actionable mutations in these tumors. The ultimate goal is to determine new therapies and optimal treatment strategy based on the genomic profile.

Keywords: small cell, genomic alteration

POSTER SESSION 1 - P1.07: SCLC/NEUROENDOCRINE TUMORS
MOLECULAR CHANGES – MONDAY, DECEMBER 5, 2016
P1.07-033 TRASTUZUMAB EMTANSMINE (T-DM1) SUPPRESSES THE GROWTH OF HER2-POSITIVE SMALL-CELL LUNG CANCER IN PRECLINICAL MODELS
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Background: To overcome chemoresistance is indispensable to bring about better prognosis in small-cell lung cancer (SCLC). We have reported that HER2 is upregulated when HER2-positive SCLC cells acquire chemoresistance. Moreover, HER2 upregulated cisplatin- or etoposide-resistant SCLC cells were sensitive to trastuzumab-mediated antibody dependent cell-mediated cytotoxicity (ADCC). However, irinotecan-resistant SCLC cells, e.g. SBC-3/SN-38, were refractory to trastuzumab despite high HER2 expression. To address this issue, we studied the antitumor efficacy of trastuzumab emtansine (T-DM1) on trastuzumab-resistant HER2-positive SCLC cells. Methods: SBC-3/SN-38 (HER2 positive) or OS2RA (HER2-negative) SCLC cells were inoculated subcutaneously in the flank of six-week-old male nude mice. Tumor size was measured with a caliper two or three times per week. When tumor volume reached about 150-200 mm3, mice were randomly assigned to three treatment groups. Each group was treated with intravenous injection of T-DM1 15 mg/kg, intraperitoneal injection of trastuzumab 30 mg/kg, or saline as control. To confirm the HER2-specific delivery of T-DM1, in vivo imaging was performed. Several tumor-bearing mice were intravenously administered with fluorescence-labeled T-DM1. Fluorescence images of mice were captured in vivo. Imaging was performed. Results: Treatment with T-DM1 significantly suppressed the growth of SBC-3/SN-38 xenografts compared with trastuzumab and saline groups. Histological analysis revealed that T-DM1 remarkably induced apoptosis and inhibited proliferation. Fluorescence–labeled T-DM1 definitely accumulated to the xenografts in a HER2-selective fashion. Conclusion: T-DM1 treatment could be an attractive therapeutic option in trastuzumab-resistant HER2-positive SCLC where trastuzumab cannot induce enough ADCC activity. Delivery of a cytotoxic agent DM1 to the inside of cells via HER2-mediated internalization is expected and crucial to exert antitumor effect in such ADCC-lacking SCLC cells.

P1.07-034 SOMATOSTATIN RECEPTORS EXPRESSION IN SMALL CELL LUNG CANCER PATIENTS
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Background: Somatostatin receptors have been described on the membrane of neoplastic cells and their expression has also been demonstrated on small cell lung cancer (SCLC). In this study we examined if the expression of somatostatin receptors at the time of disease progression correlated with survival and time to progression (TTP) of SCLC patients. Methods: 10 patients with SCLC were studied using 111In-oxitetrotide (111In-OCT) scintigraphy at diagnosis and disease progression. Scintigraphic examinations were performed following intravenous (i.v.) injection of 111MBq 111In-OCT with whole-body scintigraphy and planar scintigraphy of the thorax as well as the SPECT technique. The scintigraphic results were expressed in comparison with soft tissue intake (normal prices <1.5). Results: 111In-OCT was positive in all 10 SCLC patients at the time of diagnosis and progression of the disease. No statistical correlation was found between somatostatin receptors expression at the progression–mainly subtype 2 (SSTR 2)- and survival (p=0.43), nor TTP (p=0.25). Also the difference in somatostatin receptors expression during diagnosis and progression had no statistical correlation with survival and TTP. Conclusion: The clinical utility of receptor status characterization obtained with 111In-OCT scintigraphy is rather confined. Our study shows that 111In-OCT scintigraphy, although it is a reliable, non-invasive technique to detect primary SCLC and its locoregional or distant metastases, cannot be used as a prognostic or predictive factor in SCLC patients.

Keywords: somatostatin receptors, small cell lung cancer

POSTER SESSION 1 - P1.07: SCLC/NEUROENDOCRINE TUMORS
MOLECULAR CHANGES – MONDAY, DECEMBER 5, 2016
P1.07-035 CIRCULATING CELL-FREE TUMOR DNA (CFDNA) TESTING IN SMALL CELL LUNG CANCER
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Background: The diagnosis of small cell lung cancer (SCLC) is often made using fine needle aspiration or small biopsy of tumor specimens that are typically insufficient for next generation sequencing (NGS) analysis. Guardant360 (G360), a blood-based liquid biopsy that analyzes circulating free tumor DNA (cfDNA) and genomic alterations in plasma, provides a rapid, non-invasive method to detect SCLC. Methods: We performed a retrospective analysis of a plasma library, which contains 111 plasma samples from 54 cases of SCLC, who underwent genomic sequencing. Patients were treated at 5 tertiary care centers, between October 2012 and June 2016. The recorded data included: age at diagnosis, date of the genomic sequencing, genomic alteration (affected genes and the type of molecular alteration identified). For genomic profiling we used a platform commercially available (FoundationOne). Results: We obtained 54 samples from 54 patients. Age range is 42 to 75 years, mean 60 and median 61 years old. All cases had a histologic diagnosis of SCLC. The genomic analysis found 88 affected genes with 230 alterations. The most common affected genes: Tp53 alteration, 45 cases (83%) and Rb1 33 cases (61%). There were an average of 4.3 mutations per patient, with a median of 4 mutations per patient, with a minimum of 0 and a maximum of 13.

Conclusion: Sustained investigations and sequencing of larger numbers of SCLC are aiming to identify potential actionable mutations in these tumors. The ultimate goal is to determine new therapies and optimal treatment strategy based on the genomic profile.

Keywords: HER2, trastuzumab emtansine, SCLC, T-DM1

POSTER SESSION 1 - P1.07: SCLC/NEUROENDOCRINE TUMORS
MOLECULAR CHANGES – MONDAY, DECEMBER 5, 2016
P1.07-036 MONOCLONAL ANTIBODIES FOR HER2-AMPLIFIED TUMORS: TARGETING THE HER2 CD245 (ICAM-1) AND CD166 (FPRY) PATHWAYS FOR CANCER TREATMENT
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Background: There is no approved targeted therapy for SCLC. In order to develop targeted therapies, we need to identify and characterize the molecular targets (alterations). This study aims to report our experience with genomic sequencing of SCLC. Methods: We performed a retrospective analysis of a dataset of 54 cases of SCLC, who underwent genomic sequencing. Patients were treated at 5 tertiary referral centers, between October 2012 and June 2016. The recorded data included: age at diagnosis, date of the genomic sequencing, genomic alteration (affected genes and the type of molecular alteration identified). For genomic profiling we used a platform commercially available (FoundationOne). Results: We obtained 54 samples from 54 patients. Age range is 42 to 75 years, mean 60 and median 61 years old. All cases had a histologic diagnosis of SCLC. The genomic analysis found 88 affected genes with 230 alterations. The most common affected genes: Tp53 alteration, 45 cases (83%) and Rb1 33 cases (61%). There were an average of 4.3 mutations per patient, with a median of 4 mutations per patient, with a minimum of 0 and a maximum of 13.

Conclusion: Sustained investigations and sequencing of larger numbers of SCLC are aiming to identify potential actionable mutations in these tumors. The ultimate goal is to determine new therapies and optimal treatment strategy based on the genomic profile.

Keywords: small cell, genomic alteration
DNA, may allow the detection of potentially targetable gene abnormalities without the need for repeated tissue biopsies. Methods: Peripheral blood samples from patients with SCLC were collected in two 10 mL tubes. Cell-free DNA was extracted and analyzed by digital sequencing for the detection of single nucleotide variants (SNVs), small insertions and deletions (INDELs), Copy Number Alterations (CNAs), and gene fusions. The Tumor Alterations Relevant for Genomics-Driven Therapy (TARGET) curated database (http://www.broadinstitute.org/cancer/tga/target) was queried for potentially actionable alterations. Results: 240 samples from 227 de-identified patients were collected between June 2016 and June 2016. 7 patients had more than one sample analyzed. During this time period, the number of genes in the panel increased from 54 (10 samples) to 68 (8 samples) and finally to 70 (143 samples). The median time from sample collection to reporting was 13 days (range 8-28 days). Alterations in at least one gene were found in 222 (95.2%) of samples and 210 (92.5%) patients. SNVs in TP53 and RB1 were seen in 72.4% (152/210) and 25.7% (53/136) of patients with detectable alterations respectively. The most common potentially actionable alterations were amplifications of FGFR1 (11.8%) and ERBB2 (7.1%). MYC amplification, which was not considered an actionable alteration by TARGET but has been associated with sensitivity to Aurora kinase inhibitors in pre-clinical studies, was observed in 15.8% of patients. Eight patients had EGFR activating mutations (exon 21 L858R mutation or exon 19 deletion), of which 2 patients also had EGFR T790M mutation, likely representing transformation from NSCLC following targeted therapy with EGFR Tyrosine kinase inhibitors. KIT/PSF-ALK and AFAPI1-RET fusions were seen in 1 patient each. Conclusion: G360 is a rapid non-invasive NGS platform which may be particularly useful in patients with advanced stage SCLC where tissue samples may be suboptimal for NGS. Due to the limited treatment options in this patient population, the detection of potentially actionable genes through G360 may provide valuable information to guide treatment decisions. Keywords: small cell lung cancer, cfDNA

P1.07-036 LARGE CELL NEUROENDOCRINE CARCINOMA OF THE LUNG: THE MAYO CLINIC EXPERIENCE
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Background: Pulmonary large-cell neuroendocrine carcinoma (LCNEC) is a relatively uncommon, high-grade neuroendocrine tumor sharing several features with small-cell lung carcinoma (SCLC). LCNEC is considered aggressive, and the optimal treatment strategy and chemotherapy regimen remain undefined. Methods: We retrospectively evaluated a LCNEC patient cohort established from 1997 to 2015 at Mayo Clinic (Minnesota). A diagnosis of LCNEC was made when all WHO classification criteria were present in the tumor section examined. Clinical characteristics, treatments and outcomes were analyzed. Available radiology assessment was evaluated by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria. Results: The study included 55 LCNEC patients. Median age at diagnosis was 63 years (range: 38-88); two thirds were men; and majority were smokers (54%). Clinical staging was I, II, III or IV in 52.8%, 31%, 14.5%, and 16.3% of cases, respectively. Forty-six percent of stage IV patients presented with brain metastases at time of diagnosis (n=6/13) and 18% (n=7/38) developed brain recurrence in the follow up period. Thirty-nine (71%) patients had surgery and 9 (16%) patients received adjuvant platinum-based chemotherapy. Sixty-five percent of patients who completed resection experienced disease recurrence with 80% recurring within 2 years of resection. Treatment data for first-line palliative chemotherapy were available on 23 patients: 10 received platinum/etoposide and 13 received other regimens. In 19 patients with available imaging; the overall response rate was 52.6% (95% CI, 31.7-72.7) and there was no difference in ORR between platinum/etoposide (ORR=55.6%) or platinum plus other agents (paclitaxel or pemetrexed; ORR=55.6%). The median survival time was 26.3 months (95%CI: 18.6-33.9); the 1-, 2-, 3- and 5-year overall survival rates (OS) were 75%, 53%, 36%, and 30%, respectively. Patients who received platinum/etoposide demonstrated longer median time to progression (TTP), and median OS than those who received ‘other’ regimens (39 months vs. 21 months; p value 0.07, and 28.2 months vs. 21.1 months; p value 0.22, respectively). The differences did not reach conventional statistical significance, likely due to the small sample size. Rigorous pathologic confirmation and genomic analysis are ongoing. Conclusion: LCNEC is associated with a poor prognosis and high recurrence rates after surgery. Advanced LCNEC patients are at high risk for brain metastases, therefore, routine brain imaging surveillance during follow-up may be beneficial. The chemotherapeutic responsiveness of LCNEC patients was intermediate between that of SCLC and SCLC patients. Future prospective, multicenter, clinical trials are needed to determine the best chemotherapy regimen for these rare tumors. Keywords: lung cancer, chemotherapy, Prognosis, large cell neuroendocrine carcinoma
were re-diagnosed during 2008 to 2015 and 632 were HGNECs. NE markers, such as Syn(synaptophysin), CgA(chromogranin A) and CD56, were stained by immunohistochemistry(IHC) if morphological features were not enough for diagnoses. Results: Four were excluded due to clinical identification of transformation from adenocarcinomas to SCLC. Nine HGNECs were previously diagnosed with AC. TTF1 stained 77.4%(459/593) HGNEC patients, of which 50.6% in LCNEC, 80.9% in SCLC and 62.5% in poorly differentiated HGNEC(P<0.001). Syn staining(94.1%, 571/607) were not statistically significant in three groups(89.1% vs. 94.6% vs. 100.0%, respectively; P=0.30). The same situation was in CgA(52.6%, 319/607), with a frequency of positive staining as 46.9%, 53.6% and 25.0%(P=0.26), respectively in three diagnoses. The number of positive NE markers were generally balanced(P=0.62). Cases with zero to three positive NE markers indicated marginal significant differences of overall survival(OS)(P=0.05). Meanwhile, no differences of mOS existed in positive and negative staining of Syn(14.7 vs. 32.53 mons, P=0.14) or CgA(14.6 vs. 15.9 mons, P=0.82); but patients with typical morphological features for diagnose and thus without IHC staining Syn or CgA(mOS, 9.13mons) bore significantly poorest OS benefits than those with positive(Syn, HR=2.71, 95%CI=1.24-5.86, P=0.01; CgA, HR=2.72, 95%CI=1.25-5.92, P=0.01) or negative(Syn, HR=3.44, 95%CI=1.39-8.52, P=0.01; CgA, HR=2.76, 95%CI=1.26-6.05, P=0.01) staining. The same condition occurred especially in I to IIIa patients(P<0.01).

Conclusion: The number of positive NE markers were necessary for precise diagnoses but not significant for survival benefits. Typical morphological features of NE tumor cells were unfavorable factors for OS. Further studies are imperative to identify its crucial role in HGNEC patients.

Keywords: High grade neuroendocrine carcinoma, Neuroendocrine markers, Synaptophysin, Chromogranin A
329 deaths occurred. No statistically significant imbalance was observed in the pre-specified covariate-adjusted analyses. Results: 346 eligible patients were randomised (176 in the CE group and 170 in the IVE group) according to main evaluation criteria: best response rate (60% vs 59%, p=0.88), progression-free survival (median 5.1 vs 5.3 months, p=0.1) and overall survival times with medians of 9.6 months and 10 months and 2-year rates of 5% and 9% (p=0.16), respectively.

The following variables were statistically significantly associated with survival in univariate analysis: age (continuous evaluation) (HR=1.02, p=0.002), gender (male as reference) (HR=0.69, p=0.008), PS (PS ≤70 as reference) (HR=0.60, p=0.0001), weight loss (<5% as reference) (HR=1.28, p=0.05) and neutrophil count (<7500/mm³ as reference) (HR=1.46, p=0.003). In addition, variables with a p-value <0.2 in univariate analysis were also included in the multivariate analysis: disease extent (LD as reference) (HR=1.38, p=0.10), WBC count (<10000/mm³ as reference) (HR=1.23, p=0.08) and treatment arm (CE as reference) (HR=0.84, p=0.16).

Two variables retained their statistical significance in multivariate analysis: gender (HR=0.69, 95% CI 0.49-0.97, p=0.03) and PS (HR=0.53, 95% CI 0.49-0.97, p<0.0001). Conclusion: Adding CDDP to VP16 failed improving survival in ED SCLC. In this population, gender and performance status confirmed their prognostic value for survival.

Keywords: Prognostic factors, chemotherapy, small cell lung cancer
Background: Surgical resection is rarely possible in small-cell lung cancer (SCLC), a highly aggressive malignancy with limited treatment options. However, although in the past decades, for selected early-stage cases, a curative intent surgery has often performed, there is no biomarker to help the selection of patients eligible for surgery. Because previous studies—primarily from East Asia—showed that high neutrophil to lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) correlate with poor prognosis in several types of tumors including SCLC, the aim of our study was to investigate the prognostic value of NLR and PLR in Caucasian patients with resected SCLC. Methods: Consecutive patients with histologically confirmed and surgically resected SCLC evaluated between 2000 and 2013 at the National Koranyi Institute of Pulmonology were analyzed in this retrospective analysis. Patients were divided into “high” and “low” groups according to their NLR and PLR at diagnosis. The cut-off NLR and PLR values were 3 and 110, respectively. Next, we evaluated the associations of preoperative NLR or PLR with vascular involvement, tumor necrosis, peritumoral inflammation, tumor grade, clinicopathological characteristics (including age, gender, stage) and overall survival (OS) in univariate and multivariate analyses. Results: There were 165 patients (39 men and 26 women) with a median age of 57.7 years (range, 40-79). The pathological stages were 1, 2 and 3 in 21, 23 and 14 cases by AJCC 7th edition (in five patients no pTNM was available). PLR was high (HPLR) in 41 (63%) and low (LPLR) in 24 (37%) patients. NLR was high (HNLR) in 35 (66%) and low (LLNR) in 22 (34%) patients. PLR was significantly correlated with pathologic lymph node status (p<0.001) and NLR (p=0.007). HPLR was associated with shorter OS (vs. LLNR, HR, 2.2; 95% CI, 1.13–4.29; p=0.02). There was a non-significant trend towards longer OS in patients with HNLR (vs. LLNR, p=0.078). There were no significant associations between NLR and PLR and stage, vascular involvement, tumor necrosis, peritumoral inflammation and tumor grade. Conclusion: This is the first study in Caucasian patients with resected SCLC which shows that PLR (<110) before surgical resection may be a favorable prognostic factor for longer OS. We also conclude that preoperative HPLR may predict lymph node involvement. PLR but not NLR may have a role in selecting patients for surgery in the future. Further prospective studies are needed to confirm these observations.

Keywords: platelet-lymphocyte ratio, early-stage resected small-cell lung cancer (SCLC), neutrophil-lymphocyte ratio, prognostic factor

POSTER SESSION 1: P1.07: SCLC/NEUROENDOCRINE TUMORS
POSTER SESSION 1: P1.07: SCLC/NEUROENDOCRINE TUMORS
PROGNOSTIC FACTORS – MONDAY, DECEMBER 5, 2016

P1.07-043 PATTERNS OF FAILURE AND THE PROGNOSTIC FACTORS OF THE PATIENTS WITH LD SCLC ACCORDING TO THE TNM STAGING: TOG-TRO STUDY

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Background: The prognostic factors and patterns of relapse were retrospectively analyzed according to the TNM staging in Turkish patients with limited SCLC on behalf of Turkish Oncology Group (TOG)-Turkish Radiation Oncology Association (TROD). Methods: The data of 266 patients with limited disease SCLC from 13 multiple oncology centers who have at least 1 year follow up were analyzed. The patients were restaged according to the patients for staging. Median thoracic radiotherapy dose was 56Gy (30-66.8Gy). PCI was performed in the 180 patients (67%). The effect of age, gender, clinical stage, N stage and prophylactic cranial irradiation (PCI) on OS and DFS rates were analyzed in both univariate and multivariate analysis with Log-rank and cox regression tests. Results: Median follow up was 19 months (6-113) for the patients who were alive. Thirty-six percent of the patients had LR and approximately half of the patients developed DM. The most common metastases were seen in brain, liver and bone respectively. 2 and 5 years OS and DFS were 45.3% -20.6% and 32.2% -17.1% retrospectively. On univariate analysis, OS was significantly better in the patients with TN1,N0 tumors and clinical stage II compared to the others and patients who did not develop brain and DM and thoracic radiotherapy dose >60Gy (p=0.05). DFS was superior in patients with N0-T1 tumor, stage I-II disease, who received PCI and thoracic radiotherapy dose >60Gy (p<0.05). On multivariate analysis, PCI was found to be an independent factor affecting DFS (HR, 2.042). DM, thoracic radiotherapy dose >60Gy was a significant prognostic factor for OS (p=0.048, <0.0001 respectively). 64 patients developed brain metastases with a median 16 month (113months). Brain metastases were found to be significantly less in the patients with N0, stage I-II disease and who were treated by PCI. Conclusion: Limited disease definition includes wide spectrum of patients, therefore TNM staging should be useful in order to predict the prognosis of the patients. In our series, DFS and OS was superior for the patients with TN1 and N0 tumors than the others. Besides, the patients with TN1 and NO tumors developed fewer brain metastases, therefore PCI might be omitted for some of the patients with early staged tumor.

Keywords: limited stage, SCLC, TNM staging

POSTER SESSION 1: P1.07: SCLC/NEUROENDOCRINE TUMORS
SCLC/Neuroendocrine Tumors in General – MONDAY, DECEMBER 5, 2016

P1.07-044 EDUCATIONAL LEVEL AND MANAGEMENT IN SMALL-CELL LUNG CANCER (SCLC): A POPULATION-BASED STUDY

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Background: In a previous study we reported that educational level is a prognostic factor in SCLC, with females and LD patients with a higher educational advantage having a longer survival. In this study we examine possible associations between educational level, lead times and treatment strategies in the same cohort. Methods: The study was based on information in LCAse, a lung cancer research database generated by record linkages between the Swedish National Lung Cancer Register and several other population-based registers. Educational level was categorized according to number of years of schooling: low (<9 years), middle (10-12 years), high (>13 years). Stage was classified as limited disease (LD) and extensive disease (ED). Lead times were defined as A) from first radiological sign of a tumor to definite diagnosis and B) from date of referral from primary care to diagnosis. Treatment groups were divided as chemotherapy (CT), CT+Radiation Therapy (CT+RT), Palliative RT or no oncological therapy. Results: The study population encompassed 4278 patients with a SCLC diagnosis between 2002-2011. Median age was 69 years. 988 (23.1%) patients were diagnosed with LD (low E: 22.9%, middle E: 23.6%, high E: 26.7%); and 3187 (74.5%) with ED (low E: 74.8%, middle E: 74.0%, high E: 73.3%). One fifth of patients had a poor performance score (PS 3-4). The median lead time A was 14 days (IQR 5-32 days) and for lead time B 9 days (IQR 3-21 days). There were no differences in lead times between the educational groups. The proportion of patients receiving CT+RT was approximately 80% in LD (low E: 78.5%, middle E: 79.2%, high E: 82.4%) and 5% in ED (low E: 6.4%, middle E: 5.3%, high E: 6.8%). The percentage of patients receiving CT was 18% in LD (low E: 19.7%, middle E: 18.7%, high E: 15.3%) and 82% in ED (low E: 81.2%, middle E: 83.9% high E: 81.4%). Conclusion: There were no significant differences between educational groups in lead times or management. We conclude that the prognostic impact of educational status in Swedish SCLC patients does not appear to reflect inequalities in access to the healthcare.

Keywords: SCLC, Epidemiology, Educational level, Management

POSTER SESSION 1: P1.07: SCLC/NEUROENDOCRINE TUMORS
SCLC/Neuroendocrine Tumors in General – MONDAY, DECEMBER 5, 2016

P1.07-045 CHARACTERISTICS OF EXCEPTIONAL LONG TERM SURVIVORS IN EXTENSIVE STAGE SMALL CELL LUNG CANCER
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Background: Small cell lung cancer (SCLC) remains a frustrating disease to all parties involved. Most patients present with extensive stage disease (ED), with a median survival of 8 to 13 months (Expected). The aim of this study is to present data on survivors who lived beyond 3 years after a diagnosis of ED-SCLC (Exceptional) in order to uncover favorable factors for better patient management and clinical outcomes. Methods: We retrospectively evaluated the SCLC patient cohort diagnosed and followed from 1998 to 2012 at Mayo Clinic for Exceptional survivors (Mn/US; 2013), and selected with matched Expected survivors who had passed away within 12 months of diagnosis on age and year of diagnosis. Patient characteristics, treatments, and outcomes were compared between the two groups. Results: To date, we identified 36 Exceptional and 144 Expected SCLC patients. Women and a lower Charlson-Deyo Co-morbidity Index were more likely to be in the Expected group (p = 0.02). The overall response rate of chemotherapy was significantly higher in exceptional group (91.4% vs 56.7%, p < 0.01). Thoracic radiotherapy and prophylactic cranial irradiation (PCI) in Exceptional were also higher than in Expected group (58.3% vs 17.4%, p < 0.01, 19.4% vs 6.9%, p < 0.03). Multivariate analysis is underway. In Exceptional group, median overall survival was 5.4 years (95% CI 3.7-6.8), 9 (25%) patients were still alive. Twelve (33%) patients had disease recurrence or progression with the median progression free survival 1.2 (95% CI 0.7-2.0) years. The most common recurrent site was brain. Three patients had secondary malignancies, 2 being a non-small cell lung cancer. Conclusion: Although the chance of curing ED-SCLC is small, long-term survival can be achieved. This study supports the importance of good performance status and the achievement of a response to cisplatin-based chemotherapy on long-term survival. Addition of thoracic radiotherapy and PCI are beneficial in prolonging life of ED-SCLC patients.

Keywords: small cell lung cancer, long term survival, extensive stage, treatment

P1.07-046 UPTAKE OF RECOMMENDED TREATMENT IN SMALL CELL LUNG CANCER: TREND OVER THE LAST 15 YEARS AND RISK FACTORS
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Background: Despite the dismal outcomes of small-cell lung cancer (SCLC), the fact that SCLC patients are generally responsive to treatment emphasizes the importance of adherence to recommended treatment. This study analyzed the trend in treatment provision in SCLC over the last 15 years and its associated factors. Methods: A total of 207,375 adult patients diagnosed with SCLC between 1998 and 2012 in the United States were identified from the National Cancer Data Base. In this study, recommended treatment was defined as surgery and/or chemoradiation for the limited stage (LS-SCLC), regardless of sequence; and chemotherapy for the extensive stage (ES-SCLC). We excluded patients who did not receive treatment due to a contraindication. Logistic regression was used to analyze the risk of not receiving recommended treatment, adjusted for socio-demographics, facility type, and clinic factors. Kaplan-Meier estimator was used to estimate patients’ survival. Results: Between 1998 and 2012, the proportion of patients receiving recommended treatment increased among LS-SCLC patients (63% to 73.4%), but was unchanged in ES-SCLC (75.7% to 76.6%). Nevertheless, a significant proportion of patients did not receive recommended treatments. Older age, low income, use of non-private insurance or no insurance, higher comorbidity score, and diagnosis and/or treatment at a community cancer program were independent predictors of inadequate treatments in LS-SCLC and ES-SCLC, while Black race was a predictor only in LS-SCLC. For instance, compared to patients with private insurance, the odd ratios of uninsured patients not receiving recommended treatment or no treatment was 1.7 (95% CI 1.543-1.932) in LS-SCLC and 1.9 (95% CI 1.751-2.060) in ES-SCLC patients. Both LS-SCLC and ES-SCLC patients aged 65-74 years had 1.5 (95% CI for LS-SCLC: 1.402-1.587, 95% CI for ES-SCLC: 1.454-1.613) times higher odds of not receiving recommended treatment or no treatment, compared to younger patients. In both groups, patients who received recommended treatment had better survival than those who did not receive recommended treatment or any treatment (median survival time of 18.4 vs. 6 months in LS-SCLC, 8.3 vs. 1.2 months in ES-SCLC). Conclusion: This study demonstrated an increase in the uptake of recommended treatment in LS-SCLC, but relatively no change in ES-SCLC. Reasons for not receiving recommended treatment warrant further investigation. The survival benefit among patients with recommended treatment highlights the need to alleviate any system-based barriers that may impact more patients receiving recommended treatment.

Keywords: small cell lung cancer, survival, treatment provision
EXTENSIVE DISEASE SMALL CELL LUNG CANCER PATIENTS
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Background: The effects of first-line chemotherapy on overall survival (OS) might be confounded by subsequent therapies in patients with small-cell lung cancer (SCLC). Therefore, by using individual-level data, we aimed to determine the relationships between progression-free survival (PFS) or post-progression survival (PPS) and OS after first-line chemotherapy in patients with extensive disease SCLC (ED-SCLC) treated with carboplatin plus etoposide. Methods: Between July 1998 and December 2014, we analyzed 63 cases of patients with ED-SCLC who were eligible for PCI. Among 156 eligible patients, 99 received chemotherapy with carboplatin and etoposide as first-line chemotherapy. The relationships of PFS and PPS with OS were analyzed at the individual level. Results: Spearman rank correlation analysis and linear regression analysis showed that PPS was strongly correlated with OS (r = 0.90, < 0.05, R2 = 0.7) and PFS was moderately correlated with OS (r = 0.72, < 0.05, R2 = 0.62). Type of relapse (refractory/sensitive) and the number of regimens administered after disease progression after the first-line chemotherapy were both significantly associated with PPS (p < 0.05). Conclusion: PPS has a stronger relationship with OS than does PFS in ED-SCLC patients who have received first-line chemotherapy. In addition, type of relapse (refractory/sensitive) after first-line treatment and the number of additional regimens after first-line treatment are significant independent prognostic factors for PFS. These results suggest that treatments administered after first-line chemotherapy affect the OS of ED-SCLC patients treated with carboplatin plus etoposide.

Keywords: overall survival, post-progression survival, Progression-free survival, extensive disease small cell lung cancer

P1.07-049 LIMITED STAGE SMALL CELL LUNG CANCER: PATTERNS OF CARE AND OUTCOMES OF A SINGLE INSTITUTION OVER 15 YEARS
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Background: The past two decades have seen an increase in survival of patients with limited stage small cell lung cancer (SCLC). This retrospective audit analysed patterns of care, toxicity and survival for all patients with limited stage SCLC diagnosed and treated at Prince of Wales Hospital over 15 years. Our results were compared with the literature to assess this single institution’s performance and outcomes, and explore what factors may most be influencing these results. Methods: We identified 120 patients diagnosed with SCLC at Prince of Wales Hospital between 2000 and 2014 from the departmental electronic patient information system (Mosaic). Eligibility criteria were: age >18 years, histopathologically confirmed diagnosis of SCLC, limited stage according to the two-stage Veterans’ Affairs Lung Study Group staging criteria (2016), and treatment with either curative or palliative intent. Median progression free survival (PFS), cancer specific survival (CSS) and overall survival (OS) were estimated using the Kaplan-Meier method and log-rank test (IBM SPSS version 23.0). Results: Thirty-two patients fulfilled the eligibility criteria. The median age of patients was 66.5 years; 19 (59%) patients were female and 50% had an Eastern Cooperative Oncology Group (ECOG) score of 0. Median PFS, CSS and OS were 12.6, 22.1 and 18.0 months respectively, comparable with published literature. Ten patients (31%) received prophylactic cranial irradiation (PCI) as a component of their therapy. Of the 10 patients who received PCI, none had brain recurrence, while 36.4% of the non-PCI group developed brain metastases. Patients receiving PCI demonstrated a trend towards improved PFS compared to patients not receiving PCI (18.3 months versus 10.5 months, p = 0.057). This trend was also seen in OS in this group (25.4 months versus 15.5 months, p = 0.072). The median time from date of diagnosis to start of chemotherapy was 21 days, and there was correlation between time to chemotherapy and OS (p = 0.037) and PFS (p = 0.045). Twenty-six of the 32 patients underwent a combination of chemotherapy and radiotherapy. Seventeen patients (65%) received concurrent chemoradiotherapy, and 9 (35%) received sequential chemoradiotherapy, with no significant difference in survival or toxicity between these two regimens. Conclusion: Survival outcomes from this single institution are comparable with current literature. The use of PCI in appropriate patients can prevent cerebral metastases, improve PFS and ultimately OS. The time to initiation of chemotherapy may also have a significant impact on outcomes.

Keywords: limited stage, small cell lung cancer, cancer treatment, Survival outcomes

P1.07-050 PATTERNS OF RELAPSE IN SMALL CELL LUNG CANCER (SCLC): A RETROSPECTIVE ANALYSIS OF OUTCOMES FROM A SINGLE CANADIAN CENTER
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Background: We conducted a retrospective audit of small cell lung cancer patients (SCLC) to explore patterns of relapse and utility of Prophylactic Cranial Irradiation (PCI). Methods: A retrospective chart review was carried on patients diagnosed with SCLC from January 1st 2011 until December 31st 2014 and treated at Juravinski Cancer Center. The primary outcome was to describe the pattern of first relapse. Secondary outcomes were physician assessed response rate, overall survival (OS), utilization of PCI, time to systemic relapse (TRT) and time to central nervous system (CNS) relapse. Results: A total of 275 patients were identified, of whom 46 (16.7%) received no chemotherapy (median OS 2.2 months) and were not included in further analyses. The median age of 229 treated patients was 66 (SD 9.3) yrs. There were 115 men, 114 women. 84 (37%) had limited stage (LS) and 145 (63%) extensive stage (ES) disease, performance status (PS) was 0 in 133 (58%), PS2 in 65 (28%) and PS3 in 42 (18%). Brain metastases were present in 36 (16%) patients at diagnosis. Almost all patients received cisplatin (53%) or carboplatin (47%) plus etoposide chemotherapy. Most patients received 4 (23%), or more (52%) cycles of chemotherapy. Physician assessed RR was 68% (PR 61%, CR 7%) and 16% of patients progressed during first-line therapy. Thoracic radiation (TRT) was given to 112 (44%) of patients (LS 87%, ES 27%). Patients with brain metastases at diagnosis, or progressing during first-line chemotherapy were not considered eligible for PCI. Of all treated patients, 80 (51%) received PCI (LS 64%, ES 39%). Forty-one patients (26.3%) declined PCI. The median overall survival for all patients was 11.1m (LS 21.7m, ES 8.9m). Relapse occurred in 167 (73%) of patients: CNS alone 8.7%, CNS plus systemic relapse (13.1%), thoracic (28%), extra-thoracic (9%), thoracic/extra-thoracic (14%). Median time to any relapse was 9.2m (LS 14.3m, ES 7.5m), while median time to CNS relapse was 6.9m (PCI given 6.2m, PCI not given 4.4m). Among 50 patients with CNS relapse, 16 received PCI (LS 9, ES 7) and 34 did not (LS 5, ES 26). Among 64 patients with thoracic relapse, 31 received TRT (LS 19, ES 12) and 33 did not (LS 5, ES 28). Conclusion: Only 50% of eligible SCLC patients receive PCI. CNS relapse occurs frequently and more commonly in patients who do not receive PCI. Implementation of PCI in routine clinical practice appears to influence patterns of relapse.

Keywords: relapse, Patterns, SCLC

P1.07-051 INCIDENCE AND CLINICAL CHARACTERISTICS OF PULMONARY LARGE-CELL NEUROENDOCRINE CARCINOMA: AN OVERVIEW OF OUR OWN DATA
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Background: Pulmonary neuroendocrine tumors are a heterogeneous group of neoplasms divided into four histological types: typical carcinoid, atypical carcinoid, small-cell lung cancer (SCLC) and large-cell neuroendocrine carcinoma (LCNEC). They represent about 20% of all lung cancers. The most frequent one is small-cell lung cancer with incidence about 15%. In contrast, large-cell neuroendocrine carcinoma is an orphan disease with estimated incidence between 2% and 15%. Because of many diagnostic difficulties, LCNEC is considered to be of a higher frequency. It is lung neuroendocrine tumor, but it is also a type of non-small cell lung cancer (NSCLC). So its features overlap with both of these groups. However, the clinical behavior of LCNEC is very similar to SCLC and so new term high-grade neuroendocrine carcinoma (HGNEC) is in use. Methods: We retrospectively analysed...
patients diagnosed with cancer at our department between January 1, 2012 and December 31, 2014, with special focus on pulmonary neuroendocrine tumors. We examined incidence of different histologic types of pulmonary neuroendocrine tumors and sorted out patients with diagnosis of large-cell neuroendocrine carcinoma. We also analysed clinical characteristics of patients with LCNEC. Results: During the three-years period 1242 pulmonary patients were admitted to our department. Among them there were 734 newly diagnosed cancer patients. Various types of lung cancer were found in 652 patients. There were 104 patients with pulmonary neuroendocrine tumors, what makes about 16%. Thirteen of them (2%) were “pure” LCNEC, 16 (2,5%) mixed LCNEC with small-cell component, 68 SCLC (14%), 4 atypical carcinoid, 2 typical carcinoid and 1 typical carcinoid in patient with adenocarcinoma. Generally in our patients high-grade neuroendocrine tumors make about 15%, and low-grade neuroendocrine tumors (carcinoïdes) make only 1% of all lung cancers. Most patients diagnosed with LCNEC were men over 50 years, heavy smokers, which is consistent with published data, but one patient was a 40-year-old woman. Conclusion: Pulmonary neuroendocrine tumors are group of neoplasms classified into four categories based on their pathohistology. Three of them (carcinoïdes and LCNEC) are rare carcinoids. LCNEC is type of neuroendocrine tumor with most diagnostic and therapeutic difficulties. Clinical features of our patients are similar to previously published, while incidence is slightly lower.

Keywords: LCNEC, lung cancer, Neuroendocrine tumors

## POSTER SESSION 1 - P1.07: SCLC/NEUROENDOCRINE TUMORS

### SCLC/NEUROENDOCRINE TUMORS IN GENERAL – MONDAY, DECEMBER 5, 2016

#### P1.07-052 PULMONARY NEUROENDOCRINE TUMORS: SINGLE INSTITUTION EXPERIENCE IN BRAZIL

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Background: The primary lung neuroendocrine tumors (NET) are uncommon. They have a wide spectrum of clinical behavior, currently being classified into four types: tumor typical carcinoid (low grade malignancy), atypical carcinoid (intermediate malignancy grade), neuroendocrine large cells carcinoma and small cells. Neuroendocrine lung tumors represent a large and heterogenic group with different management and survival rates. Little information regarding neuroendocrine tumors is available for Latin American countries. Methods: Retrospective service database review of patients with NET treated at Hospital São Lucas in Porto Alegre, Brazil between 1991-2015. Inclusion criteria were age 18 or older with histologically or immunochemistry confirmed neuroendocrine tumor. For analysis purposes we divided between, typical carcinoid, atypical carcinoid and poorly differentiated (large and small cells). Results: From January of 1991 to December of 2015, of 946 lung cancer resections 49 patients with NET were resected. Most the patients were female (57,1%), mean age 55 years (28-84 years). Typical carcinoid represented 63,3% of patients, followed by atypical carcinoid (22,4%) and poorly differentiated neuroendocrine tumors (14,3%). Mean age was 51,4 for typical carcinoid, 56 for atypical carcinoid and 63 for undifferentiated NET. Lobectomy was the surgical approach for 45,5% patients, segmentectomy for 10,2% of patients. Minimally invasive (VATS) was done in 4,1%. Table 1: NET Staging

<table>
<thead>
<tr>
<th>Type</th>
<th>Stage IA</th>
<th>Stage IB</th>
<th>Stage IIA</th>
<th>Stage IIB</th>
<th>Stage IIIA</th>
<th>Stage IIIB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical carcinoid</td>
<td>10 (12.5%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Atypical carcinoid</td>
<td>0 (0%)</td>
<td>2 (25%)</td>
<td>1 (12.5%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Poorly differentiated</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
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</table>

Conclusion: According to the European Consensus, pulmonary carcinoids account for 1-2% of all invasive lung malignancies. We found 85,7% of our lung resections were carcinoids and a higher mean age 51,4 for patients with typical and 56 for atypical carcinoids compared to the literature.

Keywords: Pulmonary Neuroendocrine tumors, Carcinoids, large cells carcinoma, Small cells

#### P1.07-053 APATINIB FOR CHEMOTHERAPY-REFRACTORY EXTENSIVE STAGE SCLC: RESULTS FROM A SINGLE-CENTER RETROSPECTIVE STUDY

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Background: It has no standard treatment strategy for patients with extensive stage small cell lung cancer (SCLC) who experienced progression with three or more lines of chemotherapy. Apatinib, a new tyrosine kinase inhibitor targeting vascular endothelial growth factor receptor 2 (VEGFR-2), has been shown confirming antitumor activity and manageable toxicities in breast and gastric cancers. Until now, couple of clinical trials investigating the efficacy of apatinib on non-small cell lung cancer are ongoing. However, the effects of apatinib on small cell lung cancer are still unclear. We retrospectively assessed the efficacy and safety of apatinib in patients with extensive-stage small cell lung cancers after the failure of second or third-line chemotherapy. Methods: The study group comprised 13 patients who received oral apatinib, at a dose of 500 mg daily, for progression after the failure of second or third-line chemotherapy for extensive-stage small cell lung cancer. Treatment was continued until disease progression. For the patients who had grade 3 or 4 toxicities, the dose of apatinib was decreased to 250mg daily. The patients stopped the treatment if they still had the unacceptable toxicity after dose downregulation. We analyzed safety and response (RECIST 1.1) for the available patients monthly. Results: Between Aug 30, 2015 and May 1, 2016, 13 patients were enrolled. In 13 patients, there were 11 patients available for efficacy and safety evaluation. 5/11 (45.5%) patients experienced dose reduction during treatment. Followed up to July 20, 2016, the median duration of atapitinib treatment was 2.8 months (95% confidence interval (CI), 1.67-5.04). According to RECIST criteria, the disease control rate was 81.8%, 9/11 (partial response 18.2%, 2/11 and stable disease 63.6%, 7/11). The most frequent treatment-related adverse events were secondary hypertension (45.5%, 5/11), oral mucositis (27.3%, 3/11), hand-foot syndrome (27.3%, 3/11) and fatigue (27.3%, 3/11). Main grade 3 or 4 toxicities were hypertension (27.3%, 3/11), oral mucositis (9.1%, 1/11) and fatigue (9.1%, 1/11). Conclusion: Apatinib exhibits modest activity and acceptable toxicity for the heavily pretreated patients with extensive-stage small cell lung cancer.

Keywords: SCLC, Apatinib

#### P1.07-054 SECOND PRIMARY SMALL CELL CARCINOMA OF LUNG IN PREVIOUSLY TREATED CARCINOMA BREAST

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Background: Breast cancer is the major cause of cancer among women worldwide. Some of the patients are treated with surgery followed by adjuvant chemotherapy and radiation therapy. It is presumed that the radiation of surrounding tissues during breast radiotherapy may cause cancer in other areas of body. Methods: A 40 year old woman presented with chest pain and breathing difficulties for four months. She was diagnosed as infiltrating duct cell carcinoma of right breast and undergone modified radical mastectomy. Her 10 of 20 lymph nodes showed tumour metastases with perinodal extension. Triple marker (oestrogen receptor, progesterone receptor, her 2 neu receptor) was negative. She was given four cycles of CEF regimen cyclophosphamide, epirubicin, 5-FU) and four cycles of pacitaxel. She had received 25 fraction of radiotherapy completed over one year before. There was no other comorbid conditions, family history was not significant. She had average body built and nutrition. On general examination mild pallor was only positive finding, no peripheral lymphadenopathy or clubbing. Contrast enhanced computed tomogram of chest revealed bilateral hilar node, nodular infillity was more predominantly in left lower lobe, mediastinal lymphadenopathy with left lower lobe collapse. Ultrasound abdomen detected no significant abnormality. Bronchoscopy showed multiple nodules present over carina, infiltration in right lower lobe segmental opening, left main bronchus lumen narrowed due to diffuse infiltrative growth. The endobronchial biopsies were taken. Endobronchial biopsy revealed tumour cells were strongly and diffusely positive for synaptophysin and negative for chromogranin and TTF1. The diagnosis of small cell carcinoma lung was made. MRI of brain showed ring enhancing lesions in right cerebellar hemisphere suggestive of metastases. Staging
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P1.08-001 LOG ODDS AS A NOVEL PROGNOSTIC INDICATOR SUPERIOR TO THE NUMBER-BASED AND RATIO-BASED CATEGORY FOR NON-SMALL CELL LUNG CANCER
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Background: The paper aimed to compare the efficacy of log odds (LODDS) compared to a classification based on the number of positive lymph nodes (nN) and lymph node ratio (LNR). Methods: Material was collected retrospectively from an online survey-based database of the Polish Lung Cancer Group and included a group of 17369 patients who received radical surgical treatment (R0) due to lung cancer. The follow-up period was between 11.6 and 66.0 months (median 30.1 months). Results: In the whole group, the median survival for NO, N1 and N2 was 76.1, 41.7 and 24.2 months, respectively. The median survival for LNR in individual categories (0), (0.0-0.25), (0.25-0.55), (0.55-0.75) and (0.75-1.0) was 76.6, 48.3, 24.1, 18.8 and 16.4 months, respectively. When comparing LNR and LODDS significant heterogeneity was observed right before the IASLC abstract submission deadline, funding decisions will be made in early November 2016, so by the time of the November 11 deadline for the poster submission we will be able to include the first funded projects in the consortium in the abstract and in the poster.) Conclusion: Section not applicable

Keywords: Therapy, Early Detection, small cell lung cancer, drug resistance

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P1.08-002 THE PROGNOSTIC SIGNIFICANCE OF PLEURAL LAVAGE CYTOTOLOGY BEFORE AND AFTER LUNG RESECTION
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Background: The status of intraoperative pleural lavage cytology (PLC) has been reported to be a predictive factor of recurrence in resected non-small cell lung cancer (NSCLC). However, prognostic significance of PLC remains unclear and it has not been included in the TNM classification. Furthermore, the appropriate timing to perform PLC, before lung resection (pre-PLC) or after lung resection (post-PLC), is not evident. Methods: Of 627 consecutive patients with NSCLC who underwent complete resection (segmentectomy or more) in Tottori University Hospital from January 2004 to December 2013, 615 patients who were performed both pre-PLC and post-PLC were enrolled in this study. Patients were divided into four subgroups: (1) negative pre-PLC / negative post-PLC (Group A), (2) positive pre-PLC / negative post-PLC (Group B), (3) negative pre-PLC / positive post-PLC (Group C), and (4) positive pre-PLC / positive post-PLC (Group D). Then differences in recurrence free survival (RFS) and disease specific survival (DSS) among each groups were analyzed by log-rank test. Moreover, PLC status as a prognostic factor for RFS and DSS were analyzed using univariate and multivariate Cox regression models. Results: There were 573 patients in Group A, 11 in Group B, 14 in Group C, and 17 in Group D, respectively. Survival analysis revealed significant differences in not only RFS but also DSS between Group A and D (log-rank test, p<0.001). Group A and Group C (p<0.001), Group A and Group D (p<0.001), respectively. However, there was no significant differences among Group B, C, and D (p=0.861). Multivariate analysis identified advanced age (75+), male sex, larger tumor size (3cm), lymphnode metastasis, lymphatic invasion, and positive PLC status (Hazard Ratio: 3.735, 95% confidence interval: 2.312 to 6.063, p<0.001) as statistically independent prognostic factors for DSS. Conclusion: In conclusion, positivity of both pre-PLC and post-PLC were significant worse prognostic factor for DSS of patients with completely resected NSCLC. Therefore, surgeons should consider performing PLC both before and after lung resection to estimate patients’ prognosis correctly. Moreover, further accumulation of knowledge about PLC are needed to reflect PLC status in the TNM classification.

Keywords: lung cancer, pleural lavage cytology, prognostic factor

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P1.08-003 SURVIVAL OF LUNG CANCER PATIENTS WAS DEPENDED ON TUMOR CHARACTERISTICS, BLOOD CELL CIRCUIT, CELL RATIO FACTORS, HEMOSTASIS SYSTEM
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Background: This study aimed to determine homeostasis and tumor factors for 5-year survival (SYS) of non-small cell lung cancer (LC) patients (LCP) (T1-4N0-2M0) after complete en bloc (RO) lobectomies/pneumonectomies (LP). Methods: We analyzed data of 676 consecutive LP (age≥57±8.3 years; tumor size<4±2.4 cm) radically operated and monitored in 1985-2016 (n=585, f=91; lobectomies=431, pneumonectomies=245, mediastinal lymph node dissection=676; combined LP with resection of trachea, carina, atriun, aorta, VCS, vena azygos, pericardium, liver, diaphragm, rb, esophagus=188; only surgery=S=532, adjuvant chemoimmunoradiotherapy=AT=144; CAV= gemzar + cisplatin + thymalin/taktivin + radiotherapy 45-50Gy; T1=239, T2=249, T3=131, T4=52, N0=428, N1=130, N2=118, M0=676, G1=168, G2=202, G3=306, squamous=381, adenocarcinoma=249, large cell=44; early LC=134, invasive LC=542. Multivariate Cox modeling, clustering, SEPATH, Monte Carlo, bootstrap and neural networks computing were used to determine any significant dependence. Results: Overall life span (LS) was 2709±1692.4 days (median=1936 days) and cumulative 5-year survival (SYS) reached 69.7%, 10 years – 61.4%, 20 years – 42.9%. 419 LCP lived more than 5 years without cancer, 11–10 years, 14 – 20 years. 195 LCP died because of LC (LS=560±372.2 days). At significantly improved SYS (64.4% vs. 34.1%) (p=0.0002 by log-rank test). Conclusion: Since the tumour came to T4N2M1a according to 8th edition ofIASLC TNM classification for lung cancer. Her performance status improved to ECOG 2. She was given cisplatin and etoposide in addition to brain radiation therapy. In conclusion, positivity of both pre-PLC and post-PLC were significant worse prognostic factor for RFS and DSS were analyzed using univariate and multivariate Cox regression models. Results: In conclusion, positivity of both pre-PLC and post-PLC were significant worse prognostic factor for DSS of patients with completely resected NSCLC. Therefore, surgeons should consider performing PLC both before and after lung resection to estimate patients’ prognosis correctly. Moreover, further accumulation of knowledge about PLC are needed to reflect PLC status in the TNM classification.

Keywords: lung cancer, pleural lavage cytology, prognostic factor
test) only for LCP with N1-2. Cox modeling displayed that SYS significantly depended on: phase transition (PT) early-invasive LC in terms of synergetics, PT N0-N12, histology, G, blood cell circuit, cell ratio factors (ratio between blood cells subpopulations and cancer cells-CC), prothrombin index, heparin tolerance, recalcification time, glucose, AT (P = 0.000-0.041). Neural networks, genetic algorithm selection and bootstrap simulation revealed relationships between SYS and PT N0-N12 (rank=1), PT early-invasive LC (rank=2), eosinophils/CC (3), prothrombin index (4), thrombocytes/CC (5), glucose (6), lymphocytes/CC (7), erythrocytes/CC (8), healthy cells/CC (9), segmented neutrophils/CC (10), stick neutrophils/CC (11), monocytes/CC (12), leucocytes/CC (13). Correct prediction of SYS was 100% by neural networks computing (error=0.000, area under ROC curve=1.0). Conclusion: SYS of LCP after radical procedures significantly depended on: tumor characteristics, blood cell circuit, cell ratio factors, hemostasis system and AT.

**P1.08-004 PREDICTION OF SURGICAL OUTCOME BY MODELING BASED ON RISK FACTORS OF MORBIDITY FOLLOWING PULMONARY RESECTION FOR LUNG CANCER IN THE ELDERLY**

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Department of Thoracic Surgery II, Peking University Cancer Hospital & Institute, Beijing/China

Background: Surgical treatment for elderly patients with lung cancer presents more challenges compared with general population. The aim of the study was to predict surgical outcome following pulmonary resection for lung cancer in a single center were reviewed. Patients were divided into three ordered categories of surgical outcome according to the Clavien–Dindo classification. Using a development cohort of 401 patients, an ordinal logistic regression was performed to develop a prediction model for surgical outcome. The model was internally validated by bootstrap method and externally validated by another cohort of 124 patients. Two previous models were reviewed.

**Models c-statistic (95%CI) Hosmer-Lemeshow test**

<table>
<thead>
<tr>
<th>Model</th>
<th>c-statistic (95%CI)</th>
<th>Hosmer-Lemeshow test</th>
</tr>
</thead>
<tbody>
<tr>
<td>The present model</td>
<td>0.75 (0.69-0.80)</td>
<td>0.674</td>
</tr>
<tr>
<td>After bootstrapping</td>
<td>0.75 (0.68-0.80)</td>
<td>0.671</td>
</tr>
<tr>
<td>External validation</td>
<td>0.70 (0.64-0.75)</td>
<td>0.382</td>
</tr>
<tr>
<td>Kates, M. et al (2009)</td>
<td>0.63 (0.57-0.69)</td>
<td>0.115</td>
</tr>
<tr>
<td>Poullis, M. et al (2013)</td>
<td>0.61 (0.54-0.67)</td>
<td>0.091</td>
</tr>
</tbody>
</table>

Conclusion: Our model displayed an acceptable ability to predict surgical outcome in elderly patients undergoing pulmonary resection for lung cancer.

Keywords: morbidity, lung cancer, Surgery, elderly

**P1.08-005 STRATIFICATION OF PSTAGE I LUNG ADENOCARCINOMA BY THE SCORING SYSTEM BASED ON PROGNOSTIC FACTORS**

Naoyuki Kawakita, Hiroaki Toba, Toru Sawada, Mitsuhiro Tsuboi, Koichiro Kajura, Yukikiko Kamawaka, Mitsuiteru Yoshida, Hirotsmi Takizawa, Kazuya Kondo, Akira Tangoku
Department of Thoracic and Endocrine Surgery and Oncology, Institute of Health Biosciences, the University of Tokushima Graduate School, Tokushima/Japan

Background: In stage I lung cancer, tumor size and PL factors are only reflected by the TNM staging system. However, other clinicopathological factors have the potential to influence recurrence and prognosis, especially in stage I lung adenocarcinoma. This study aimed to evaluate prognostic factors, and to thereby stratify stage I lung adenocarcinoma patients.

Methods: A total of 203 patients who underwent curative resection for stage I invasive adenocarcinoma, from 2006 to 2013, were retrospectively reviewed. 13C-Fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) was performed in 194 patients and the maximum standardized uptake value (SUVmax) of the tumor was calculated. Invasive adenocarcinoma was classified into 3 predominant subtypes (lepidic, papillary, and others) according to the IASLC/ATS/ERS classification. The associations between various clinicopathological factors and recurrence were evaluated, and disease-free survival (DFS) was analyzed. Results: Twenty-eight patients had recurrent disease during the follow-up period (mean; 59.3±25 months). Univariable analysis showed male gender, smoking history ≥20 pack-years, BMI≥20, CEA>5ng/ml, T classification, tumor size, tumor stage, and SUVmax to be significantly associated with worse DFS. Multivariable analysis showed male gender (P=0.008), papillary predominant histologic subtype (P=0.023), other predominant (P=0.008), and SUVmax (P=0.008) were extracted as independent prognostic factors associated with worse DFS. Predictive variables were scored as follows; tumor size≥20mm (1 point), papillary predominant (1 point), other predominant (2 points) and SUVmax≥3.0 (1 point). Patients were classified into 3 risk groups (low-risk: 0-2, intermediate-risk: 3, high-risk: 4) according to their aggregate scores. The 5-year DFS rate was 91% in the low-risk group, 55% in the intermediate group and 36% in the high-risk group. The 5-year DFS rates during the same period in our institute were 88% in pStage IA, 69.5% in pStage IB, 53% in pStage II, and 38% in pStage IIIA patients. Therefore, the DFS rate in the intermediate-risk group was comparable to that of pStage II, and the DFS rate in the high-risk group was comparable to that of pStage IIIA. Conclusion: In stage I lung adenocarcinoma, tumor size, SUVmax and histologic subtypes were suggested to be prognostic factors. This scoring system may predict the groups, such as patients with pStage II and IIIA, requiring platinum based post-operative chemotherapy.

Keywords: Adenocarcinoma, Prognostic factors, Surgery

**P1.08-006 PROGNOSTIC IMPACT OF INCOMPLETELY LOBULATED FISSURES IN NON-_SMALL-CELL LUNG CANCER**

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Background: The division of the incompletely lobulated fissures is often performed during the surgical resection of non-small-cell lung cancer (NSCLC). However, the influence of lobulation on tumor recurrence was unclear in these patients. Therefore, we assessed the prognostic impact of lobulation in patients with NSCLC. Methods: A retrospective study of patients with NSCLC who underwent lobectomy and bi-lobectomy was conducted between April 2008 and May 2016. Patients who underwent division of the interlobar fissure using stapling devices were compared with those who did not undergo division of the interlobar fissure. Results: A total of 126 patients with NSCLC (from p-stage IIA to IIIA) who underwent surgery with (n = 103) or without (n = 23) division of the interlobar fissure were included in this analysis. No significant between-group differences were observed with respect to most variables, except for operation side (p = 0.0483), operation time (p = 0.0469), and post-operative lung comorbidity (p = 0.0033). Survival analysis revealed a significant between-group difference in disease-specific survival (DSS, P = 0.0334); however, no significant differences were observed with respect to disease-free survival (p = 0.1372) and overall survival (p = 0.0666). Cox regression univariate analysis revealed a significant association between DSS and the number of staplers used to divide the interlobar fissure (p = 0.0486). Conclusion: In this study, the extent and status of the incompletely lobulated fissure...
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P1.08-007 The Significant Improvement of Lung Function After Preoperative Rehabilitation in Patients with Thoracic Tumors and Abnormal Spirometry

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Background: The evaluation of degree of improvement of exercise tolerance and rest lung function parameters after preoperative pulmonary rehabilitation in patients with thoracic tumors and baseline borderline abnormal spirometry results. Methods: Clinical inclusion criteria were: diagnosis of thoracic tumors and reduced values of FEV1 and FVC predicting postoperative complications.

We observed 29 patients (16 women, 13 men) in mean age of 68 (range 57-68) years. Spirometry, six minute walking test distance (6MWT) and maximum metabolic equivalent during exercise on treadmill (MET) were chosen for evaluation of lung function and physical function during rehabilitation. The tests were performed twice during screening phase to eliminate the factors of learning, and were repeated after first and second week of rehabilitation. Pulmonary rehabilitation included two weeks of training on the treadmill with individually selected speed, physiotherapy exercises as breathing training with using of Triflo. Results: The significant differences were observed after pulmonary rehabilitation: 1). FEV1 (L): 1.41±1.58 vs 2.61±1.90 (p=0.0000027) 2). FEV1 (%N): 60.49±71.49 vs 86.03±10.96 (p=0.0000021) 3). FVC (L): 2.34±2.64 vs 3.61±1.40 (p=0.0000020) 4). FVC (%N): 79 vs 95 (p=0.0000269) 5). 6MWT Distance (m): 350 vs 400 (p=0.0000027) 6). MET: 2.66±2.90 vs 3.20±2.95 (p=0.000007) Conclusion: A two-week pulmonary rehabilitation leads to significantly improvement of lung function and physical performance in patients with thoracic tumors and borderline abnormal spirometry results which may provide significantly better outcome of patients in short- and long-time follow-up.

Keywords: pulmonary rehabilitation, Lung function test

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P1.08-008 Impact of Perioperative Redox Balance on Long-Term Outcome in Patients Undergoing Lung Resection

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Background: Surgical stress provokes a cytokine storm and systemic inflammatory response syndrome, and can also affect redox balance during the postoperative course. However, whether inflammatory status, especially redox balance, during the perioperative period has an effect on long-term outcome following surgery for lung cancer remains unclear. The aim of this study was to determine whether redox balance during the perioperative period is associated with long-term survival of patients after undergoing lung resection. Methods: Consecutive patients who underwent an anatomical lung resection. This study was performed to evaluate outcome in

characteristic curve revealed a dROM cut-off value of 327 during the operation. Patients with a dROM value of 327 or less showed significantly superior 3-year survival as compared to those with a greater value (87.5% vs. 20.0%, p<0.001). Conclusion: Surgical stress caused an increase in dROM during the postoperative course. The dROM value obtained during the operation was correlated with long-term survival of patients after undergoing resection for lung cancer.

Keywords: Surgery, NSCLC, Lobulation, Prognosis

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P1.08-009 Does Body Mass Index (BMI) Affect Outcomes Post Lung Resection Surgery?

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Background: Increased BMI increases the surgical risk, atelectasis and postoperative complications in patients considered obese (BMI>30). Several published studies have shown a protective effect of increased BMI. The introduction of Enhanced Recovery Programme (ERP) in surgical units has greatly benefited obese patients in other surgical specialties but its impact in patients undergoing thoracic surgery is uncertain. We looked at the outcomes of patients at our unit since its implementation. Methods: A retrospective cohort study was performed on all patients undergoing first time lobectomies for primary lung cancer between January 2015-June 2016. Patients with BMI<18 were excluded from the study. Student’s T-test, Mann-Whitney-U Test and Chi-Squared analysis was used for statistical analysis of demographics and outcomes. Results:

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P1.08-010 Octogenarians Perform Equally to Younger Patients in Lung Cancer Surgery

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1Department of Hematology and Oncology, Medical University Innsbruck, Innsbruck/Austria, 2Department of Visceral, Transplant and Thoracic Surgery, Medical University Innsbruck, Innsbruck/Austria

Background: Due to prolonged life expectancy, more patients aged 80 years or older will be diagnosed with lung cancer and eventually undergo anatomic lung resection. This study was performed to evaluate outcome in

Preoperatively, the FEV1 and DLCO were both significantly higher in patients with BMI≥30. There were no statistically significant postoperative differences between the two groups. Patients with a BMI<30 can do just as well as patients with BMI≥30 in an ERP for patients with lung cancer undergoing lobectomy.

Keywords: BMI, Lobectomy, Obesity, NSCLC

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P1.08-011 OCTOGENARIANS PERFORM EQUALLY TO YOUNGER PATIENTS IN LUNG CANCER SURGERY

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1Department of Hematology and Oncology, Medical University Innsbruck, Innsbruck/Austria, 2Department of Visceral, Transplant and Thoracic Surgery, Medical University Innsbruck, Innsbruck/Austria

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Keywords: BMI, Lobectomy, Obesity, NSCLC
surgically treated octogenarians compared to younger patients. Methods: The institutional database of all consecutive patients treated between 2009 and 2015 was analysed. The age cut-off was set at 80 years. Perioperative and follow-up data were compared between the two groups. Results: A total of 453 patients were treated by a VATS approach at our center for proven NSCLC. 28 (6.2%) patients were aged 80 or older. There was no difference in gender distribution, clinical T stage, preoperative FEV1/FVC and preoperative haemoglobin values. Clinical N stage was higher in the octogenarians (p=0.049). Median operative time was 175 minutes in the younger patients compared to 156 minutes in the octogenarians (p=0.104). Neither tumor diameter nor distribution of tumor histology showed any significant difference between the two groups. Postoperative haemoglobin values as a surrogate parameter for intraoperative complications were comparable between the groups. Median hospital stay was 10 days in both groups (p=0.634). There was no in-hospital mortality in the octogenarians. Disease free (72.1 vs. 58.4 months, p=0.673) and overall survival (81.7 vs. 83.8 months, p=0.456) did not show any significant difference between octogenarians and younger patients.

Conclusion: Lung resection can safely be performed in selected octogenarians with acceptable morbidity and low mortality rates. In our experience it is even as safe as in younger patients. Our data adds evidence that in such patients potentially curative treatment should not be withheld.

Keywords: octogenarians, VATS

P1.08-012 CHARACTERIZING TIME TO CARE FOR LUNG CANCER SURGICAL PATIENTS
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Background: The Kelowna Thoracic Surgical Group (KTSG), centered in Kelowna, British Columbia (BC), Canada provides care to a geographic area of 807,538 km². This is 85% of the province of BC and approximately 9 times the size of Austria. A significant portion of this population consists of remote and rural communities. Ensuring equal and prompt access to lung cancer diagnosis and treatment regardless of proximity to treatment center is important not only because of the time sensitivity of care, but also because of the overall healthcare burden of this highly prevalent and often lethal malignancy. Methods: A retrospective chart review was performed on all patients seen by the KTSG who came to definitive surgical treatment in Kelowna for a diagnosed or suspected lung cancer between January 2010 and December 2015. Dates were collected at three time-points along the care pathway: Referral, Consult, and Surgical Treatment. We calculated times from referral to consult (RC), consult to treatment (CT), and overall referral to treatment (RT). Demographic information was collected for each of the patients and the distances patients lived from the Surgical Centre were determined. The study has received approval from both University of British Columbia – BC Cancer Agency and Interior Health Authority research ethics boards. Results: There were 902 patients in the cohort; 446 local patients who lived within a radius of 100 km or less from Kelowna and 456 distant patients who resided further than 100 km from the city. For the entire group, the median RT was 50.5 days comprised of RC = 6 days, and CT = 44 days. For the local patient group, the median RT was 49 (Interquartile Range (IQR) = 33.75 to 60) days compared to a median of 52.5 (IQR = 36 to 52.5) days for the distant patients. The extreme overlap in the IQR shows no significant clinical difference in time to care between the local and distant patients. Conclusion: Time from referral to treatment for patients with suspected or confirmed lung cancer seen by the KTSG is similar for both local and distant patients. The equitable times to care with the IHTSG suggests that the current model of patient-doctor communication provides a growing opportunity to mitigate the impact of distance on access to care.

Keywords: Health Equity, Thoracic Surgery, Time to Care
Background: Chronic obstructive pulmonary disease (COPD) is related to the prognosis of patients with lung cancer, and one of risk factors of respiratory complications after surgical resections. This study aimed to investigate whether perioperative inhalations of long-acting beta-agonists (LABAs) or long-acting muscarinic antagonists (LAMAs) would decrease the postoperative complications in lung cancer patients with COPD. Methods: We retrospectively analyzed 108 patients with COPD who underwent pulmonary resections for primary lung cancer at our hospital between January 2013 and January 2016, in order to determine the association between the incidence of postoperative complications (e.g., prolonged air leakage and pneumonia) and the use of LABAs or LAMAs. Results: Among 108 patients with COPD patients, there were 86 men and 22 women, with a mean age of 69.3 years (range, 46–84). The mean FEV1/FVC was 61.4% (range, 26.8%-69.9%). The surgical procedures were partial resection in 11 patients, pulmonary segmentectomy in 3 patients, lobectomy in 92 patients, and pneumonectomy in 2 patients. The histological types showed adenocarcinoma in 53 patients, squamous cell carcinoma in 38 patients, adenosquamous carcinoma in 5 patients, large cell neuroendocrine carcinoma in 3 patients, large cell carcinoma in 4 patients, small cell carcinoma in one patient, and pleomorphic carcinoma in 4 patients. There were 29 postoperative complications in COPD (26.9%), prolonged air leak (more than 7 days) 16 cases, pneumonia 9 cases, arrhythmia 2 cases, chylothorax 2 cases, wound infection 2 cases. The frequency of postoperative pulmonary complications such as prolonged air leakage and pneumonia, was significant higher in COPD (23 cases, 21.3%) than in non COPD (15 cases, 6.7%). Inhaled bronchodilators such as LAMA or LABA were prescribed to 34 cases in COPD, not to 74 cases. The pulmonary complications were significant lower in LABA or LABA users (3 cases, 8.8%) than in no users (20 cases, 27.0%). Conclusion: For lung cancer patients with COPD, preoperative management using the inhalants with LABA or LAMA, and smoking cessation can reduce the frequency of the postoperative pulmonary complications after surgical lung resection. The inhalants with LABA or LAMA may be adapted for the management of not only perioperative care but also long-term survival of COPD patients after surgery.

Keywords: Chronic obstructive pulmonary disease, lung cancer, Long-acting beta-agonist, Long-acting muscarinic antagonist

P1.08-014 USEFULNESS OF CHEST CT IN FOLLOW-UP OF PATIENTS WITH COMPLETELY RESECTED LUNG CANCER

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1Thoracic Surgery, Ac Camargo Cancer Center, São Paulo/Brazil, 2Ac Camargo Cancer Center, São Paulo/Brazil

Background: There is no consensus about the best method to follow up patients after complete resection of lung cancer. This study was performed to identify how often follow-up chest-CT detected recurrence or a second primary lung cancer in asymptomatic patients. Methods: This is a retrospective study. Patients with diagnosis of non-small cell lung cancer submitted to complete surgical resection were included. They were followed-up with regular visits to the clinic and chest CTs. The visits to the clinic were every three months in the first two years, semiannually up to the fifth year, and annually thereafter. Patients were classified in symptomatic and asymptomatic according to the presence of clinical manifestations at each visit. Results: From 2003 to 2013, 134 patients were included. Median age was 63.5 years. Seventy three (54.5%) were male. Current or former-smokers were 70.1% of the patients. Adenocarcinoma was the most common histologic type, observed in 82 (61.2%) of the patients. Lobectomy/lobectomy was performed in 79 (73.8%), segmentectomy in 31 (23.1%), and pneumonectomy in 4 (3%). Pathological stage was: IA (53%), IB (10.2%), IIA (17.1%), IIB (6.6%), IIIA (13.3%), IIIB (3.3%), and IV (2.1%). Forty six (44.3%) patients were submitted to adjuvant treatment. Median follow-up was 30.2 months. Recurrence was detected in 18 (13.4%) patients, being local (including mediastinal nodes) in 10 (7.4%), and distant in 8 (5.9%). Local recurrences were mainly detected by chest CT and second primary lung cancers in asymptomatic patients. Distant recurrence was detected mostly by clinical symptoms (Table 1). Second primary lung cancers were found by chest CT

in 15 (11.2%) asymptomatic patients. Table 1 – Correlation between type of recurrence and presence of symptoms.

<table>
<thead>
<tr>
<th>Type of Recurrence</th>
<th>Local recurrence</th>
<th>Distant recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT (Asymptomatic)</td>
<td>9 (90%)</td>
<td>2 (25%)</td>
</tr>
<tr>
<td>CT (Symptomatic)</td>
<td>1 (10%)</td>
<td>6 (75%)</td>
</tr>
<tr>
<td>Total</td>
<td>10 (100%)</td>
<td>8 (100%)</td>
</tr>
</tbody>
</table>

P1.08-015 SURGERY OF STAGE I NON-SMALL CELL LUNG CANCER IN PATIENTS AGED 80 YEARS OR OLDER

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Surgery, Onomichi Municipal Hospital, Onomichi/Japan

Background: Non-small cell lung cancer (NSCLC) is a typical disease of the elderly patients, and is becoming increasingly. Surgical resection is standard treatment for early-stage NSCLC. We evaluate the efficacy of lobectomy versus segmentectomy for stage I non-small cell lung cancer in elderly patients 80 years or older. Methods: 54 cases with stage I of 82 patients aged 80 years or older who underwent surgery for non-small cell lung cancer at our hospital between 2004 and 2013 were studied. The patients’ medical records were reviewed with type of operation, histological diagnosis, postoperative morbidity, postoperative mortality and survival results. Results: There were 33 men and 21 women. The average ages were 83.4 years (range, 80-90 years). Adenocarcinoma was identified in 45 patients and squamous cell carcinoma was identified 9 patients. Lobectomy was performed in 25 patients for stage IA (n=10) and IB (n=15), segmentectomy was performed in 18 patients for stage IA (n=15) and IB (n=3) and wedge resection was performed in 11 patients for stage IA (n=10) and IB (n=1). Mean follow-up was 53 months. 4 cases of 54 patients died for lung cancer and 8 cases died for other causes within 5 years after lung resection. Overall survival rate at 5 years in all patients was 70.6%. One case of 25 patients who underwent lobectomy died for lung cancer (IA n=1, IB n=0), 3 cases died for other causes (IA n=1, IB n=2). Two cases of 18 patients who underwent segmentectomy died for lung cancer (IA n=0, IB n=2), 3 cases died for other causes (IA n=2, IB n=1). Overall survival rate at 5 years for lobectomy versus segmentectomy was 74.5% vs 68.1% (IA; 67.5% vs 86.7%, IB; 77.0% vs 0%). Mortality rate in all patients was 22.2% (lobectomy: 20.0% vs segmentectomy: 27.8%), atrial fibrillation 5 patients (3 vs 2), heart failure 1 patient (0 vs 1), prolonged air leakage 3 patients (1 vs 2), atelectasis 2 patients (0 vs 2), delirium 1 patient (1 vs 0). Mortality rate was 0% in both groups. Conclusion: The lobectomy and segmentectomy were equal results in elderly patients 80 years or older for stage IA NSCLC. These data further support the use of lobectomy for resection of stage IB tumors.

Keywords: 80 years or older, Early-stage NSCLC, segmentectomy
Mean age of male patients was 68.±9.5 years and female patients was 66.7±9.0 years. The median length of stay for males and females were 8 (Q1=6, Q3=12) and 7 (Q1=6, Q3=10) days respectively. The Chi squared test for trend for males showed X²(1)=0.07, 2p=0.8, females showed X²(1)=0.00, 2p=1.0. There was no statistical difference for both males and females BMI distribution between the SHS and our cohort.

### Table. Multivariate analysis of Overall Survival & Disease Free Survival

<table>
<thead>
<tr>
<th>Variables</th>
<th>HR</th>
<th>p</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Survival</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>2.243</td>
<td>0.003</td>
<td>1.323-3.801</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>age &lt; 60</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>60 ≤ age &lt;70</td>
<td>2.647</td>
<td>&lt;0.001</td>
<td>1.593-4.298</td>
</tr>
<tr>
<td>70 ≤ age</td>
<td>4.637</td>
<td>&lt;0.001</td>
<td>2.605-8.149</td>
</tr>
<tr>
<td>p-N stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N1+N2</td>
<td>1.809</td>
<td>0.003</td>
<td>1.231-2.660</td>
</tr>
<tr>
<td>Recurrence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>5.377</td>
<td>&lt;0.001</td>
<td>3.316-8.719</td>
</tr>
<tr>
<td>Disease free survival</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p-N stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N1+N2</td>
<td>2.609</td>
<td>0.017</td>
<td>1.190-5.719</td>
</tr>
</tbody>
</table>

Conclusion: This study confirmed that late recurrence occurred in patients with no recurrence for 5 years after surgical resection, and it had a negative effect on overall survival beyond 5 years after operation. Furthermore, N positive (N1 or N2) was an independent risk factor for both overall survival and disease free survival. Therefore, careful follow-up is needed for the detection of late recurrence even in patients with five years disease free survival, and especially for node-positive patients. More studies are needed to clarify this.

Keywords: early stage NSCLC, LN dissection
Abstracts

P1.08-019 RISK FACTORS AND SURVIVAL OF OCCULT N2 LYMPH NODE METASTASIS IN NSCLC PATIENTS WITH CLINICAL N0-1 DIAGNOSED BY PROPERED PATHO-CT

Keywords: NSCLC, occult N2 LN metastasis

P1.08-020 THE EFFECT OF TWO INTERVENTIONS ON ATTAINMENT OF SURGICAL QUALITY MEASURES IN RESECTED NON-SMALL CELL LUNG CANCER (NSCLC)

Keywords: quality improvement, non-small cell lung cancer, intervention

P1.08-021 PREDICTORS OF POST-OPERATIVE MORTALITY IN NON-TEXAS NSCLC PATIENTS - MONDAY, DECEMBER 5, 2016

Keywords: long term survivor with 5 years disease free, late recurrence risk factor, positive N stage, non-small cell lung cancer

Conclusion: The combined effect of two interventions to improve pathologic lymph node examination has a greater effect on attainment of a range of surgical quality parameters than either intervention alone.

Keywords: quality improvement, non-small cell lung cancer, intervention study, Surgical resection
SMALL CELL LUNG CANCER (NSCLC) IN A HIGH MORTALITY REGION OF THE US

Matthew Smeltzer1, Yu-Sheng Lee1, Edward Robbins1, Nicholas Faris1, Chris Mutrie1, Meredith Ray1, Sam Signore1, Carrie Fehnel1, Cheryl Houston-Harris2, Meghan Meadows1, Raymond Osaigbgon1

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Background: Surgical resection is recommended for most patients with early-stage NSCLC. High postoperative mortality risk diminishes the benefit of curative-intent surgery. We examined factors associated with mortality within 120 days of curative-intent resection in a population-based cohort. Methods: We examined all NSCLC patients with curative-intent resections from 2009-2016 in all 11 hospitals in 4 US Dartmouth Referral Regions. We evaluated patient demographics, disease characteristics, pre-operative evaluation, treatment, and perioperative complications to identify risk factors for 30-, 60-, 90-, and 120-day mortality using logistic regression models. Results: The 2,258 patients’ median age was 67, 48% were female; 78% were White, 21% Black. The 30-, 60-, 90-, and 120-day post-operative mortality rates were 6%, 8%, 8%, and 9%. After adjusting for all other factors, American Society of Anesthesiologists score (ASA) (p=0.0035), prior lung cancer (p=0.0406), and Charlson comorbidity score (p=0.0163) were associated with 30-day mortality. Adjusted models for 120-day mortality indicate associations with age (p=0.0001), tumor size (>4cm) had 26.5% 120-day mortality. Although patients with all three risk factors (age >75, Charlson score >=3, tumor >4cm) had 2.7 times the odds of 120-day mortality by 12%. Patients with all three risk factors (age >75, Charlson score >=3, tumor >4cm) had 2.7 times the odds of 120-day mortality compared with those <49. A Charlson score >3 (vs. 0) conferred 1.5 times the odds of 120-day mortality compared with those <49. A Charlson score >3 (vs. 0) conferred 1.5 times the odds of 120-day mortality compared with those <49. A Charlson score >3 (vs. 0) conferred 1.5 times the odds of 120-day mortality compared with those <49. A Charlson score >3 (vs. 0) conferred 1.5 times the odds of 120-day mortality compared with those <49. A Charlson score >3 (vs. 0) conferred 1.5 times the odds of 120-day mortality compared with those <49. A Charlson score >3 (vs. 0) conferred 1.5 times the odds of 120-day mortality compared with those <49. A Charlson score >3 (vs. 0) conferred 1.5 times the odds of 120-day mortality compared with those <49. A Charlson score >3 (vs. 0) conferred 1.5 times the odds of 120-day mortality compared with those <49. A Charlson score >3 (vs. 0) conferred 1.5 times the odds of 120-day mortality compared with those <49.

Conclusion: Age, ASA, Charlson score, and tumor size are important risk factors for post-operative mortality. Inter-hospital disparity suggests an opportunity for institution-level corrective interventions. Patients with the combination of age >75, Charlson score >3, and advanced T-category had a high rate of post-operative mortality.

Keywords: Surgical resection, Early-stage NSCLC, Post-operative Mortality
Background: Pulmonary adenocarcinoma (ASC) is a rare neoplasm and factors affecting survival after pulmonary resection, as well as its clinical and pathologic characteristics, are still unknown. For a better understanding we reviewed our large experience with these patients. Methods: Records of 134 patients (108 men, median age: 65 years) with diagnosis of ASC operated on between January 1999 and May 2015 were retrospectively analyzed from a prospective database; survival was calculated by using Kaplan-Meier method. Results: 86 patients (64.1%) were smokers. Median tumor size was 4.8 cm (range, 0.6 to 23 cm). Initial histological diagnosis was NSCLC in 88 cases, adenocarcinoma in 21, pleomorphic tumor in 13, and no diagnosis in 12. 62 patients (66.0%) received a platinum-based induction chemotherapy. Surgery included lobectomy in 87 patients (65%), pneumonectomy in 27 (20.1%), wedge resection in 12 (8.9%), and segmentectomy in 8 (6%). Four patients (3%) had an incomplete resection. Postoperative staging included 45 stage I (33.6%), 47 stage II (35.1%), and 42 stage III (31.3%). 64 patients (47.7%) received adjuvant treatment. Five-year overall survival and disease-free survival were 36.6% and 35.7%, respectively (median, 28 and 18 months, respectively). Recurrences occurred in 76 patients (56.7%) most of them at distant sites (67/76 [81.8%]). Factors associated with increased survival included no smoking habit (p = 0.02), no induction therapy (p = 0.04), right side disease (p = 0.01), pathological stage I (p = 0.001), no metastatic lymph nodes (p = 0.001), and adjuvant treatment (p = 0.003). At multivariate analysis, pN0, pstage I, and adjuvant treatment were independent prognostic factors (p = 0.02, 95% CI 1.54-6.43, p = 0.03, 95% CI 1.23-7.32, p = 0.001, 95% CI: 1.26-4.72, respectively). Conclusion: PPC are aggressive tumors usually presented as a large lesion in males. Preoperative diagnosis remains difficult. Prognosis is poor, and distant recurrence rate is high. Long-term survival can be achieved in early stage disease and by an appropriate adjuvant therapy.

Keywords: lung tumor, Pleomorphic carcinoma

Background: Adenosquamous carcinoma (ASC) of the lung is a rare pulmonary disease with poor prognosis. We evaluated the prognostic factors and outcome of this tumour. Methods: Records of patients undergoing pulmonary resection for ASC between 1998 through 2015 were reviewed using a prospective database. 124 patients (91 men, median age, 67 years) with ASC were operated on. Results: Surgical procedures included 3 exploratory thoracotomies, 6 bilobectomies, 76 lobectomies, 19 pneumonectomies, 12 induction chemotherapy. Surgery included lobectomy in 87 patients (65%), pneumonectomy in 27 (20.1%), wedge resection in 12 (8.9%), and segmentectomy in 8 (6%). Four patients (3%) had an incomplete resection. Postoperative staging included 45 stage I (33.6%), 47 stage II (35.1%), and 42 stage III (31.3%). 64 patients (47.7%) received adjuvant treatment. Five-year overall survival and disease-free survival were 36.6% and 35.7%, respectively (median, 28 and 18 months, respectively). Recurrences occurred in 76 patients (56.7%) most of them at distant sites (67/76 [81.8%]). Factors associated with increased survival included no smoking habit (p = 0.02), no induction therapy (p = 0.04), right side disease (p = 0.01), pathological stage I (p = 0.001), no metastatic lymph nodes (p = 0.001), and adjuvant treatment (p = 0.003). At multivariate analysis, pN0, pstage I, and adjuvant treatment were independent prognostic factors (p = 0.02, 95% CI 1.54-6.43, p = 0.03, 95% CI 1.23-7.32, p = 0.001, 95% CI: 1.26-4.72, respectively). Conclusion: PPC are aggressive tumors usually presented as a large lesion in males. Preoperative diagnosis remains difficult. Prognosis is poor, and distant recurrence rate is high. Long-term survival can be achieved in early stage disease and by an appropriate adjuvant therapy.

Keywords: lung tumor, Pleomorphic carcinoma

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Keywords: lung tumor, Pleomorphic carcinoma

Background: Lung cancer is the leading cause of cancer death worldwide. The long-term survival is an important outcome of oncologic therapies. In early stages, permits to evaluate the quality of surgical oncology services, meanwhile in advanced stages the quality of the multidisciplinary teams. Screening programs and early diagnosis are the most efficient way to achieve increase in overall survival. The results of Clínica Santa María in Lung Cancer patients are presented. Methods: All patients diagnosed with Non-small Lung Cancer, treated by the team of Thoracic Surgery in our private hospital, during the period January 2011 to July 2016 were entered prospectively, consecutively and daily to a web database. Demographic, clinical and pathological data, as well as monitoring all events were recorded. All our patients underwent to an exhaustive staging process. Statistical descriptive analysis of clinical and demographic variables and 5 year overall survival are shown. Results: 313 patients were included, median age of 65 years old (32-89), 48,6% female. Adenocarcinoma was the most frequent histology (78,9%), Stage I 48,6%, Stage II 5,27%, Stage III 14,8%, and Stage IV 26,5%. The median follow-up time was 50 months (1-283) with a mean survival time of 99 months. Overall 5-year survival was 63,7% (95%CI, 57-69%), and by stages: Stage I 91,4% (95%CI, 84,9-95,2%), Stage II 63,7% (95%CI, 39,5-80,3%), Stage III 44,3% (95%CI, 26,4-60,8%) and Stage IV 19,1% (95%CI, 10,1-30,3%). Adenocarcinomas was 64% (95%CI, 56,6-70,5%).

Keywords: lung cancer, Survival, Non-small cell lung cancer
P1.08-027 EVOLUTION OF SURVIVAL IN A REGIONAL POPULATION-BASED US LUNG CANCER RESECTION COHORT
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Background: Quality variances in surgical resection and pathology examination practice translate into survival disparity in patients with early stage lung cancer after curative-intent resection. We evaluated the survival patients from two eras in a US regional cohort. Methods: All curative-intent lung cancer resections in 11 US hospitals in 4 contiguous Dartmouth Hospital Referral Regions were analyzed for stage-stratified survival before and after an ongoing regional quality improvement campaign started in 2009. Overall and stage-stratified survival of patients with surgery in the 2004-2009 (pre-era) vs 2010-2015 (post-era) were compared using the log-rank test and Cox proportional hazards models. Results: Of the total cohort of 3246 patients, 40.6% were in the earlier era, 59.4% in the later era. Demographic characteristics were similar between cohorts (Table 1). Preoperative PET/CT, brain MRI scans, bronchoscopy, and adjuvant therapy were more frequently used in the later era. Patients in the early era had an unadjusted hazard ratio (HR) of 1.22 (p<0.0006). After controlling for stage, tumor size, neoadjuvant therapy, comorbidity score, grade, extent of surgery, patients in the pre-era had a HR of 1.49 (p<0.0001).

Conclusion: Survival has improved since introduction of a regional quality improvement campaign in a high lung cancer mortality region of the US.

Keywords: Lung cancer survival, non-small cell lung cancer, Surgical resection, quality improvement

P1.08-028 NATIONWIDE TRENDS IN SURGERY FOR LUNG CANCER IN FINLAND FROM 2004 TO 2014
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Background: Surgical treatment for lung cancer has developed in recent decades and has enabled surgical treatment of patients with increasingly severe comorbidities. The aim of this study is to describe nationwide trends in lung surgery: incidence of surgical treatment, operative mortality, changes in surgical approaches, long term survival and predictors thereof in Finland between 2004 and 2014. Methods: Patients with any type of lung surgery and pre- or postoperative diagnosis of C34.9 were identified from the national

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Background: Primary salivary gland type tumors of lung (PSGTTL) are rare intrathoracic malignant neoplasm. Their description in literature is largely limited to a few case series/case reports. We herewith present our surgical experience and offer more confidently to more patients with heavier disease burden.

Keywords: Surgery, outcomes, lung cancer

P1.08-039 SURGICAL EXPERIENCE OF PRIMARY SALIVARY GLAND TUMORS OF LUNG: EXPERIENCE FROM TERTIARY CARE CENTER IN NORTH INDIA

Ashish Jakkhetiya,1 Pankaj Garg,1 Surayaranayana Deva,2 Nooan Shukla,3 Durgatosh Pandey,1 Mukudripi Ray,1 Prabhat Malik,1 Deepalji Jain,1 Sunil Kumar1
1Surgical Oncology, All India Institute of Medical Sciences, New Delhi/India, 2Surgical Oncology, All India Institute of Medical Sciences and University College of Medical Sciences, New Delhi/India, 3Pathology, All India Institute of Medical Sciences, New Delhi/India

Background: Primary salivary gland type tumors of lung (PSGTTL) are rare intrathoracic malignant neoplasm. Their description in literature is largely limited to a few case series/case reports. We herewith present our surgical experience and offer more confidently to more patients with heavier disease burden.

Keywords: Surgery, outcomes, lung cancer

P1.08-031 NON-SMALL CELL LUNG CANCER IN PATIENTS AGED 40 YEARS OR YOUNGER: CLINICAL, SURGICAL, AND LONG-TERM OUTCOMES

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1Thoracic Surgery, University of Milan, Milan/Italy, 2Thoracic Surgery, University Hospital of Lung Diseases, Tirana/Albania, 3Thoracic Surgery, University Hospital of Lung Diseases, Tirana/Albania, 4Pneumology, University Hospital of Lung Disease ‘Shefqi Ndroqi’, Tirana/Albania

Background: Non-small cell lung cancer (NSCLC) in young patients is uncommon and has clinical characteristics different from that in older patients. We report the outcomes of a single institutional experience in the treatment of young patients with NSCLC. Methods: Records of patients with NSCLC operated on between 1998 and 2013 were retrospectively analyzed.

Keywords: female lung cancer, Surgery

P1.08-030 FEMALE LUNG CANCER AND OUR FIVE YEAR EXPERIENCE

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Background: Lung cancer is one of the leading causes of mortality in the world. The incidence of lung cancer in females is increasing at a substantially faster rate than that seen in males. However, according to a lot of publications, lung cancer is almost six times more frequent in men than in women. The literature shows clearly that lung cancer in women differs from that in men in several aspects and environmental factors and lifestyle plays an important role in the female lung carcinogenesis. The objectives of this study were to evaluate clinic-morphologic features of lung cancer in women and the role of the surgery in their treatment. Methods: This was a descriptive retrospective study, conducted for five years. We analyzed all patients hospitalized diagnosed and treated for lung cancer and using Pearson Chi-Square test. Results: The ratio men to women for patients diagnosed with lung cancer was 8:1. The most common histotype was Adenocarcinoma 76%, Squamous cell carcinoma 11%, Small cell carcinoma 5%, others 8%. The average age was 57.5 with 50-62 years. 6% of females were in I stage, 22% of them were in II stage, 15% of them were in IIIA stage, 10% of them in IIIB stage and 47% in IV stage. Only 5% of our patients were smokers. Dyspnea was the main clinical sign, found in 67% of women. The standardized incidence of female lung cancer patients was 5/100.000. The surgery was performed in 20% of them meanwhile in men it was performed in 12.5% of cases. Conclusion: Most of women diagnosed with lung cancer in advanced stages were smokers. The most common histotype. This study shows that lung cancer in female is eight time less frequent in women than in men. Since the ratio men to women regarding to being operable is in the favor of women because they are diagnosed earlier comparing to men, women are more subject of surgery. Because the clinical signs of lung cancer are far from being specific, a substantial portion of lung cancer cases and deaths could be prevented by applying effective prevention measures, such as tobacco control and the use of early detection tests.

Keywords: female lung cancer, Surgery

P1.08-042 MALIGNANT TUMORS WITH ENDOBRONCHIAL GROWTH: CLINICAL AND PATHOLOGICAL ASSESSMENT AND MANAGEMENT

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Background: Malignant tumors with endobronchial growth are being series specific, a substantial portion of lung cancer cases and deaths could be prevented by applying effective prevention measures, such as tobacco control and the use of early detection tests.

Keywords: adenoid cystic carcinoma, mucoepidermoid carcinoma, Primary salivary gland type tumors of lung
Clinicopathological factors were reviewed for time to recurrence (TTR), and recurrence patterns were compared according to oncogenic status and examined according to EGFR mutational subtype. Results: Among 401 patients, 185 with EGFR mutation, 46 with KRAS mutation, 15 with ALK rearrangement, and 155 with triple negative mutation (TN) were identified. Multivariate analysis following univariate analyses showed that younger age, well–moderately differentiated histology, earlier pathologic stage, and presence of EGFR or ALK mutation were favorable prognostic factors for TTR. Locoregional recurrence was observed in 53.3% of ALK-positive patients, being significantly common in these patients than in EGFR- and KRAS-positive patients. EGFR-positive patients mostly experienced pleural recurrence, the incidence of which was significantly higher in TN patients. Adrenal recurrence was observed in 7.2% of TN patients, but it was rarely identified in EGFR-positive patients. (Figure) Among EGFR-positive patients, the incidence of brain metastases was significantly higher in L858R cohort than in Del Ex19 cohort.

Conclusion: In resected NSCLC, younger age, well–moderately differentiated histology, earlier pathologic stage, and presence of EGFR or ALK mutation were favorable factors for TTR, and distinct recurrence patterns were revealed according to oncogenic mutation status and mutational EGFR subtype. Our results may provide suggestions for developing a strategy for follow-up and adjuvant therapies after resection.

Keywords: recurrence, oncogenic status
P1.08-033 EFFECT OF EGFR MUTATIONS ON SURVIVAL IN PATIENTS FOLLOWING SURGICAL RESSECTION OF LUNG ADENOCARCINOMA
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Background: While numerous trials have evaluated the effects of EGFR mutations on survival in patients undergoing treatment with tyrosine kinase inhibitors (TKIs), research on the influence of EGFR mutations in patients undergoing surgical resection as their primary intervention is limited and conflicting. We hypothesized that patients with resectable EGFR-mutant tumors have a better postoperative prognosis than those with wild-type (WT) tumors, as EGFR-mutant tumors often include an in-situ component that portends an improved prognosis. We further hypothesized that the two most common EGFR mutations may impact post-resection prognosis differentially.

Methods: We carried out a single-center, retrospective study evaluating the influence of EGFR mutation status on progression-free (PFS) and overall survival (OS) after resection, adjusting for tumor stage and ethnicity. Kaplan-Meier plots and Cox proportional hazard models were used to generate crude and adjusted hazard ratios. Results: 249 patients underwent lung adenocarcinoma resection and had mutational analysis and ≥1 year of follow-up at our institution between 2008-2016. These resections included 200 lobectomies, 12 segmentectomies, and 32 wedge resections. Ninety-three (37.3%) patients had EGFR-mutant tumors. Relative to WT tumors, EGFR-mutant tumors were more likely to exhibit well-differentiated (44.0% vs 29.0%; p=0.009) or lepidic (61.3% vs 36.5%; p=0.0001) histology, and trended towards pT stage IA (p=0.082). EGFR mutation improved crude OS (HR 0.39, 95% CI 0.15-0.93; p=0.034), but this difference became nonsignificant when adjusted for tumor stage and ethnicity (OS HR 0.549, 95% CI 0.20-1.058; p=0.245). PFS did not differ between mutant and WT cohorts (adjusted HR 0.94, 95% CI 0.350-1.603; p=0.817). In comparing L858R and Exon 19, neither PFS (adjusted HR 0.91, 95% CI 0.350-2.379; p=0.851) nor OS (HR 0.88, HR 0.10-1.740; p=0.879) significantly differed. Lastly, sublobar resection did not interact with EGFR mutation presence to affect PFS (interaction p-value=0.735) or OS (interaction p-value=0.771).

Conclusion: Patients with EGFR-mutant adenocarcinomas exhibit improved crude post-resection OS vs. those with WT tumors, but this difference disappears after adjustment for tumor stage and ethnicity. These findings appear attributable to EGFR-mutant tumors presenting at earlier stages. We hypothesize that this occurs because lepidic tumors spread a longer phase in stage I before developing a more aggressive phenotype. Our finding that EGFR mutation is associated with an improved post-resection OS (sublobar vs. ≥lobar) suggests that mutation status should not affect surgical planning prior to resection.

Keywords: EGFR, lung adenocarcinoma, sublobar resection

P1.08-034 PROGNOSTIC IMPACT OF EGFR MUTATION IN PATIENTS WITH SURGICALLY RESECTED LUNG ADENOCARCINOMA: ANALYSIS ABOUT SUBTYPES OF EGFR MUTATIONS
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Background: Epidermal growth factor receptor (EGFR) gene mutations have an important role for predicting the prognosis in advanced or recurrent lung cancer patients. However, the significance of EGFR mutation as a prognostic factor for survival after complete resection remains controversial. The aim of this study is to evaluate the impact of mutational status in patients with surgically resected lung adenocarcinoma. Methods: We retrospectively investigated the data of 446 patients (pts) with surgically resected lung adenocarcinoma who underwent completely tumor resection in our hospital from 2009 to 2013. Overall survival (OS), disease-free survival (DFS), and clinicopathological factors affecting these factors were evaluated. Results: There were 202 males and 212 females (median age, 67 years). In total, 270 (65%), 66 (16%) and 78 (19%) had p-stage I, II and IIIA disease respectively. In all 210 pts (51%) with EGFR mutation were detected. Eighty-six pts (21%) had exon 19 deletion (19 del) and 113 pts (27%), exon 21 mutation (L858R). Among 414 pts, 131 pts (31%) had lung cancer recurrence. The median follow-up period was 38.6 months. p-stage mutant/wild:145/125, II/24/42, and IIIA/41/37. The 3-year survival rates of p-II and IIIA mutant/wild were 96.8%/92.1% and 81.6%/81.8% respectively. The median survival time of p-stage IIIA mutant was 80.5 months, and those of others were not reached. The 3-year DFS of p-II and IIIA mutant/wild were 83%/69.2% and 27%/16.5%, respectively. There were no significant difference in OS and DFS at each p-stage despite the EGFR mutational status. Compared to the wild type, the p-IIIA mutant group had a poor DFS. Conversely, compared to wild type, the p-I mutant group showed a favorable DFS. According to the subtypes of EGFR mutation, there were no significant differences among EGFR subtypes, but pts with 19del tended to have the worst DFS. In subgroup analysis of 131 pts with recurrence, 3-year survival rate of p-II and IIIA mutant/wild were 92%/75.8% and 80%/45.6% respectively. Pts with p-IIIA mutant showed significantly favorable OS than those of wild type (p=0.014) as well as with p-II wild type. Although OS was not significantly different among the subtypes of EGFR mutation, pts with 19del showed statistically better prognosis than shown by the wild type (p=0.038). Conclusion: EGFR status was an independent prognostic factor in pts with surgically resected lung adenocarcinoma. Particularly, EGFR exon 19 deletion might be the strongest predictive factor of poor DFS and good OS in resected lung adenocarcinoma.

Keywords: lung adenocarcinoma, Epidermal growth factor receptor, exon 19 deletion

P1.08-035 ANALYSIS OF POST-OPERATIVE RECURRENCE IN A POPULATION WITH NSCLC HARBORING AN EGFR MUTATION: A SINGLE INSTITUTIONAL RETROSPECTIVE STUDY
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Background: The post-operative recurrence in the patients resected EGFR mutated NSCLC was higher than wild-type, as previous reported. However, whether EGFR mutational status is prognostic factor or not had not been yet proven, and we assessed the background of the patients with surgically resected NSCLC harboring EGFR mutation and the post-operative clinical course. Methods: We reviewed all patients with EGFR mutated NSCLC who received surgical therapy for lung cancer between March 2007 and April 2016 at Matsuoka Municipal Hospital in order to assess post-operative recurrence and overall survival retrospectively. Survival curves of time to post-operative recurrence and overall survival were calculated using the Kaplan-Meier method and were compared using the log-rank test. Subgroup analyses were conducted to evaluate predictive factors for post-operative recurrence. Results: A total of 116 patients were enrolled. The median age was 72.5, ranging from 37-88 years of age. Of the total, 83 patients (71.6%) were female, and 30 patients had never smoked. All patients except one with squamous cell carcinoma were diagnosed pathologically with adenocarcinoma. Of the patients 41.9% were diagnosed with Ex19 deletion and 50.0% were diagnosed with Ex21L858R. Median time to post-operative recurrence was 70.5 months for the entire population. Multivariate analysis revealed that age (p=0.008), subtype of EGFR mutation (p=0.034), and pathological stage (p=0.0033) were predictive factors for post-operative recurrence. Subgroup analysis revealed there was a significant difference in time to post-operative recurrence between patients over 75 y.o and those under 74 y.o even in the population who received a lobectomy. (p=0.031) Conclusion: Elderly patients, and the small sample size, further investigations are warranted to confirm these results.

Keywords: NSCLC, EGFR mutation, Post-Operative Recurrence

P1.08-036 THORACOTOMY AND VATS SURGERY IN LOCAL NON-SMALL CELL LUNG CANCER: DIFFERENCES IN LONG-TERM HEALTH
POSTER SESSION 1: P1.08: SURGERY
Minimal Invasive Surgery - MONDAY, DECEMBER 5, 2016

A research question that you identified as requiring further study was: How do thoracotomy and VATS differ in the long-term health outcomes for patients with locally advanced non-small cell lung cancer? The study design included a retrospective analysis of patients who underwent either thoracotomy or VATS surgery for the treatment of non-small cell lung cancer. Patients were divided into thoracotomy (n=100) and VATS (n=150) groups. The primary outcome measure was long-term survival, defined as the time from surgery to the date of death or last follow-up. Secondary outcomes included quality of life assessments, time to recurrence, and overall survival rates. The study population consisted of patients with stage I-III non-small cell lung cancer, excluding stage IV disease. Thoracotomy was more commonly used for patients with larger tumors (≥3 cm) and those with more extensive lymph node involvement. VATS, on the other hand, was associated with a lower rate of complications and a shorter hospital stay. The long-term survival rates for patients undergoing thoracotomy and VATS were compared using the Kaplan-Meier method and were found to be statistically significant (p<0.05). The study conclusions were that VATS surgery offers improved long-term survival compared to thoracotomy. However, further research is needed to confirm these findings and to explore other factors that may influence long-term outcomes.
RELATED QUALITY OF LIFE

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Background: Older and more fragile NSCLC patients are operated on through video-assisted thoracic surgery (VATS), compared to thoracotomy. In this study we compare the long-term health related quality of life (HRQoL) among early stage and locally advanced NSCLC patients between these two operative methods. Methods: 687 NSCLC patients underwent lobectomy or segmentectomy in our clinic between January 2000 and January 2013, of these 430 were operated before July 2009 and 257 after this. HRQoL questionnaire 1SD was sent to patients alive in June 2011 and February 2016 (min. 2 years from operation). After the exclusion of patients with clinically extensive disease (T4, N2 or M1), lacking data (n=5) or receiving neoadjuvant therapy, 345 (19±154) patients were included in the study. Results: 289 (84%) patients answered, 152 from the first and 133 from the second period. Respectively, 42 and 68 respondents had had VATS. The two groups differed in the following features: thoracotomy group had on average more advanced clinical and pathological stage (26% vs 7% and 28% vs 16% stage II & III, respectively), younger age at operation (63.9 vs 66.8 years), and higher frequency of adjuvant therapy (18% vs 5%) (p<0.05 in each). The VATS group scored statistically (p<0.05) and clinically significantly lower on the dimensions Breathings (0.63 vs 0.70), Excretion (0.78 vs 0.85), Usual activities (0.75 vs 0.81), Mental function (0.83 vs 0.89), Depression (0.82 vs 0.88), Distress (0.82 vs 0.88), Vitality (0.76 vs 0.82), Sexual activity (0.72 vs 0.80) and on the 15D score representing overall HRQoL (0.81 vs 0.85) (Figure).

Conclusion: Even with less invasive surgical techniques, the older and more comorbid patients seem to have lower long-term HRQoL. This is contrary to previous results of short-term reports.

Keywords: NSCLC, HRQoL, Surgery, Long-term

POSTER SESSION I - P1.08: SURGERY MINIMAL INVASIVE SURGERY - MONDAY, DECEMBER 5, 2016

P1.08-038 VATS SUB-LOBAR ANATOMICAL PULMONARY RESECTIONS: INDICATIONS AND OUTCOMES IN THORACIC ONCOLOGICAL PRACTICE

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Background: In patients with limited pulmonary reserve, sub-lobar anatomical pulmonary resection (SLAPR) may have reduced perioperative morbidity and mortality and additionally may better preserve long-term pulmonary function compared to lobectomy. SLAPR may also mitigate the oncological deficiencies of wedge resection. However, the safety and oncological efficacy of video assisted thoracoscopic surgical (VATS) SLAPR has not been well described. We therefore audited our recent experience of VATS SLAPR to evaluate: indications, safety, and oncological outcomes. Methods: We retrospectively reviewed a prospectively maintained database to identify all consecutive patients who underwent planned VATS SLAPR with curative intent. Demographics, co-morbidities, indications and treatment outcomes were retrieved, with supplemental chart review where necessary. Results: Seventy seven VATS SLAPRs were performed between December 2010 and May 2016. Median age of patients was 67 (44–83) years and 57% (44/77) were male. The majority (47/77, 61%) of SLAPRs were undertaken for resection of NSCLC. Indications for SLAPR in NSCLC patients included: inadequate pulmonary reserve (DLCO <60% or predicted post-operative DLCO <40%) in 21/77 (27%), excessive (≥2 major) comorbidities in 18/77 (24%), advanced age (>75 years) in 13/67 (27%) or a combination of these factors precluding lobectomy. In patients with metastatic 22 (28%) and benign 8 (10%) nodules, indications included proximity to vascular structures or inability to palpate lesion precluding simple wedge resections. Superior segmentectomy (22/77, 28%) and lingula sparing left upper lobectomy (17/77, 22%) were the commonest SLAPR performed. Seventy one (92%) were completed via VATS. Emergency conversion occurred in one case. Morbidity rate was 30% (23/77) and 30 day mortality rate was 2.5% (2/77). Pre-operative DLCO was not associated with post-operative pulmonary complication (P=0.7) or length of hospital stay (P=0.20). In the NSCLC sub group, all patients were clinically stage I; R0 resection was achieved in 100%. Median of 12 (6–27) nodes were excised with a nodal upstaging rate of 25% (12/47) and pathological stage was I in 65%. Median disease free survival (DFS) was 40 months and median overall survival (OS) was not reached. Loco-regional recurrence rate was zero. Pre-operative DLCO dichotomised using median did not correlate with OS (P=0.8) or DFS (P=0.29). Conclusion: A variety of VATS SLAPRs may be performed safely with acceptable morbidity and mortality in high risk patients. Complete microscopic resection and adequate nodal dissection can be achieved. Although larger studies and longer follow is needed, our findings suggest that VATS SLAPR achieves comparable oncological outcomes in high risk patients to formal lobectomy.

Keywords: Sub-lobar anatomic pulmonary resection, Video-assisted thoracoscopic surgery

POSTER SESSION I - P1.08: SURGERY MINIMAL INVASIVE SURGERY - MONDAY, DECEMBER 5, 2016

P1.08-037 THORACOSCOPIC SEGMENTECTOMY OF PULMONARY NODULES AFTER COMPUTED TOMOGRAPHY-ASSISTED BRONCHOSCOPIC METALLIC COIL MARKING (2ND VERSION)

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Background: With advances in computed tomography (CT), small pulmonary lesions previously unseen on chest radiographs are being increasingly detected. Among lesions less than 10 mm in size, a considerable number of malignancies have been reported. To localize small and deeply situated pulmonary nodules during thoracoscopic fluoroscopy, we developed a marking procedure that uses a metallic coil and a coin for thoracoscopic segmentectomy. Methods: Fifteen patients underwent thoracoscopic segmentectomy under fluoroscopic and monitor, which aided in nodule manipulation. Nodules were completely resected under thoracoscopic guidance. Results: The marking procedure took 11 to 49 minutes from insertion to removal of the bronchoscope. There were no complications from the marking, and all 16 nodules were easily localized by means of thoracoscopy. The metallic coil showed the nodules on the fluoroscopic RD monitor, which aided in nodule manipulation. Nodules were completely resected under thoracoscopic guidance in segmentectomy. The pathologic diagnosis was primary adenocarcinoma in 10 nodules, pulmonary metastases in 3 nodules, an atypical adenomatous hyperplasia in 1 nodule, a hamartoma in 1 nodule and a nontuberculous mycobacteriosis in 1 nodule. One case of adenocarcinoma in situ with an extensive two segments was performed a curative segmentectomy. Conclusion: In this study, CT-guided transbronchial metallic coil marking with an ultrathin bronchoscope with a coin on a patient’s chest wall under bi-planar fluoroscopy after CT-assisted stimulation was found to be feasible and safe. In our previous report, CT had been needed at least three times, but this method needed only twice CT scan. It might be a useful method not only for making a diagnosis but also for therapeutic resection in selected early lung cancers.

Keywords: VATS, coil marking, CT assisted bronchoscopy, segmentectomy
P1.08-039 SYSTEMATIC REVIEW AND UPDATED META-ANALYSIS OF UNIPORTAL VERSUS MULTIPORTAL VIDEO-ASSISTED THORACOSCOPIC SURGERY FOR LUNG CANCER

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Background: Uniportal video-assisted thoracoscopic surgery (VATS) is a challenging surgical procedure that poses substantial technical difficulties compared to multiportal VATS but has been associated with favorable outcomes in studies reported to date. Methods: On-line databases were screened until June 2016. Meta-analysis aimed to compare clinical outcomes of uniporal and multiportal VATS lobectomy for patients with lung cancer. Endpoints assessed included perioperative mortality, operative time and blood loss; length of hospital stay; duration of postoperative drainage; rates of conversion to open thoracotomy; number of harvested lymph nodes and overall morbidity. Risk Ratios (RR)/Mean Difference (MD) and corresponding 95% Confidence Intervals (95%CIs) served as primary statistics. Results: Twelve studies were included (among them 1 randomized trial) that enrolled N=2,476 patients. There was no difference in the 30-day mortality: (N=2,476); RR (95%CIs) 0.32 (0.03-3.01); p=0.32; Event rates: 0.10% (1/1,021) vs 0.07% (1/1,455); no difference were demonstrated for conversion to thoracotomy: 0.31 (0.48-1.73); p=0.77; similarly there were no differences in regard to operative times: MD (95%CIs): 3.50 (12.35-19.34) min; p=0.67 and blood loss: 2.15 (1713-12.83) ml; p=0.78. There was no statistically significant difference between number of harvested lymph nodes: 18.4±6.6 vs 19.4±8.5; MD (95%CIs): -0.34 (-1.39-0.70) node; p=0.52. Uniporal VATS was associated with significantly shorter duration of chest tube drainage: -0.61 (-0.99-[-0.23]) days; p=0.002 (Figure 1A); and length of hospital stay: -0.58 (-0.77-[-0.40]) days; p=0.001 (Figure 1B). Overall morbidity was significantly reduced with uniporal VATS as well: RR (95%CIs) 0.77 (0.63-0.95); p=0.01.

Conclusion: Uniporal VATS is at least as safe and effective as multiportal VATS for patients with lung cancer. Whether clear postoperative benefits with uniportal VATS further translate into reduction of clinical endpoints and potentially improved survival remains to be confirmed in adequately powered randomized trial.

Keywords: VATS lobectomy, uniporal VATS, meta-analysis, VATS segmentectomy

Figure 1. Individual and summary point estimates. Uniporal vs multiportal VATS. Length of hospital stay (A) and duration of chest tube drainage (B). Conclusion: Uniporal VATS is at least as safe and effective as multiportal VATS for patients with lung cancer. Whether clear postoperative benefits with uniportal VATS further translate into reduction of clinical endpoints and potentially improved survival remains to be confirmed in adequately powered randomized trial.
**P1.08-040 LYMPH NODE SAMPLING IN 3-PORT VIDEO ASSISTED THORACOSCOPIC SURGERY (VATS) VS UNIPORTAL VATS**

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Background: VATS is fast overtaking thoracotomy as the approach to lobectomies due to faster recovery times. Uniportal VATS lobectomies are slowly becoming more popular throughout the world but the advantages of Uniportal VATS over the standard 3-port approach is unclear. The lung resection can often be performed via a Uniportal approach although concurrent lymphadenectomy/lymph node sampling, may be more challenging. We explored the adequacy of lymph node sampling at our unit as per the ESTS 2006 guidelines on intraoperative lymph node staging. Methods: All Primary Lung Cancers (Non-small cell lung cancers) performed by 4 VATS surgeons from May 2015-July 2016 were included in the study. A single surgeon performed all the Uniportal VATS lobectomies. The standard 3-port approach was employed by 4 VATS surgeons. Patient demographic details and length of stay were obtained from our Cardiothoracic Database (CaTH) alongside pathological findings. Results:

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<th>Details</th>
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<th>Standard (n=149)</th>
<th>p-value</th>
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<tr>
<td>Age</td>
<td>67.5±3.77</td>
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<tr>
<td>Height (cm)</td>
<td>167.7±5.73</td>
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<td>Weight (kg)</td>
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<td>71.35±16.15</td>
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<tr>
<td>Perctd (DL/COPY)</td>
<td>90.4±21.36</td>
<td>88.7±21.85</td>
<td>0.734</td>
</tr>
<tr>
<td>Reparacy</td>
<td>Volume in 1 sec (n/mm²)</td>
<td>19±17</td>
<td>6.8±6.6</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>19/17</td>
<td>68/86</td>
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<tr>
<td>Thoracocore</td>
<td>1.20±0.50</td>
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<tr>
<td>Side Left/Right</td>
<td>13/23</td>
<td>64/35</td>
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<tr>
<td>Staging (AJCC)</td>
<td>16 (53.3%)</td>
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<tr>
<td>Stage 1a</td>
<td>11 (36.6%)</td>
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<td>Stage 1b</td>
<td>5 (16.6%)</td>
<td>15 (10.1%)</td>
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<tr>
<td>Stage 2b</td>
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<td>Compliant to ESTS 2006</td>
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</table>

Conclusion: Overall and disease free survival are not influenced by the type of surgical approach. Due to perioperative benefits with shorter length of hospital stay and less complications, a minimally invasive approach as the gold standard of surgical treatment for clinically nodal negative lung cancer patients should be advocated.

Keywords: VATS, early lung cancer, overall survival

**P1.08-042 OVERALL SURVIVAL AND TUMOR RECURRENCE AFTER VATS LOBECTOMY OF N1 POSITIVE NSCLC IS EQUAL TO OPEN RESECTION**

Herbert Maier, Caecilia Ng, Florian Kocher, Magdalena Sach, Gregor Laimer, Paolo Lucciarini, Thomas Schmid, Florian Augustin

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Background: Video-assisted thoracoscopic surgery (VATS) is an accepted alternative to open resection for early stage non-small cell lung cancer. This study was performed to analyze survival after primary VATS anatomic resection for nodal positive NSCLC compared to an open approach. Methods: The prospective institutional VATS database was searched for pT1 patients after primary surgery for NSCLC (62/504 patients between February 2009 and December 2015). Exclusion criteria were neoadjuvant treatment and conversion to thoracotomy. Demographics and survival were compared to a historic group of N1 positive patients, who underwent primary open surgery via a standard posterolateral thoracotomy for lung cancer between 2002 and 2007 (57 patients). Results: Age (65 vs 61.5 years), gender and stage distribution (UICC IIA vs IIIA) did not differ between the VATS and open group. Half of the patients in the VATS group had clinical stage NO (31/62) confirmed by PET-CT. More people received adjuvant therapy after VATS lobectomy (50/62 vs 31/57, p=0.003). Median follow up was 22 months in the VATS group and 47 months in the open group (p<0.0001). Disease recurrence occurred in 16/62 and 22/57 patients after a median of 13 and 12 months, respectively, (p=0.1692). Overall survival did not differ between the two groups (Figure 1, log rank, p=0.4006). No survival difference was found between unforeseen and clinically evident nodal positive patients in the VATS group (p=0.9686).

Conclusion: Overall and disease free survival are not influenced by the type of surgical approach. Due to perioperative benefits with shorter length of hospital stay and less complications, a minimally invasive approach as the gold standard of surgical treatment for clinically nodal negative lung cancer patients should be advocated.

Keywords: VATS, early lung cancer, overall survival

**P1.08-041 DISEASE FREE AND OVERALL SURVIVAL IS EQUAL IN OPEN AND VATS RESECTION FOR EARLY LUNG CANCER IN A MULTIVARIATE ANALYSIS**

Caecilia Ng, Florian Kocher, Herbert Maier, Magdalena Sach, Gregor Laimer, Michael Fiegl, Paolo Lucciarini, Thomas Schmid, Florian Augustin

1Department of Visceral, Transplant and Thoracic Surgery, Medical University Innsbruck, Innsbruck/Austria, 2Department of Hematology and Oncology, Medical University Innsbruck, Innsbruck/Austria

Background: Video-assisted thoracic surgery (VATS) has become a valid alternative to open resection for lung cancer treatment. However, robust data on the oncologic equality are still missing. This study evaluates disease free and overall survival for patients with early stage (cN0) lung cancer treated either with open or VATS resection. Methods: A total of 359 patients with early stage (cN0) lung cancer with available survival data in our institutional database were treated between 2004 and 2015. VATS was introduced in 2009, since that time all clinically nodal negative patients were treated with an intended VATS approach. Results: There were 198 male patients; median age was 65 (range 38-85) years. 256 (71.3%) patients were treated with a minimally invasive approach. There were significantly more female patients (p=0.002) and lower pt-stages (p=0.002) in the VATS group. Nodal upstaging was found in 19.1% in the VATS group and 23.3% in the open group (p=0.486). 5-year disease free survival was 61.2% in the VATS group and 63.8% in the open group (p=0.492). 5-year overall survival was 84.3% in the VATS group and 73.3% in the open group (p=0.139), Figure 1. In a multivariate analysis including age, gender, pt-status, pn-status and surgical approach, none of the factors proved to independently predict disease free survival. In overall survival, a positive pn status was found to be the only independent negative prognostic factor (HR: 2.2, 95% CI: 1.2-4.1).

The patients in the standard cohort had a higher ThoracoScore indicating increased risk of surgery. There was no statistically significant demographic difference between the two groups. The rate of lymph node dissection was similar in both groups. Conclusion: Despite the perceived limited access, uniportal VATS has shown to be as good as standard 3 port VATS for lymph node sampling intraoperatively.

Keywords: lobectomy, uniportal, VATS

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**P1.08-040 DISEASE FREE AND OVERALL SURVIVAL IS EQUAL IN OPEN AND VATS RESECTION FOR EARLY LUNG CANCER IN A MULTIVARIATE ANALYSIS**

Caecilia Ng, Florian Kocher, Herbert Maier, Magdalena Sach, Gregor Laimer, Michael Fiegl, Paolo Lucciarini, Thomas Schmid, Florian Augustin

1Department of Visceral, Transplant and Thoracic Surgery, Medical University Innsbruck, Innsbruck/Austria, 2Department of Hematology and Oncology, Medical University Innsbruck, Innsbruck/Austria

Background: Video-assisted thoracoscopic surgery (VATS) has become a valid alternative to open resection for lung cancer treatment. However, robust data on the oncologic equality are still missing. This study evaluates disease free and overall survival for patients with early stage (cN0) lung cancer treated either with open or VATS resection. Methods: A total of 359 patients with early stage (cN0) lung cancer with available survival data in our institutional database were treated between 2004 and 2015. VATS was introduced in 2009, since that time all clinically nodal negative patients were treated with an intended VATS approach. Results: There were 198 male patients; median age was 65 (range 38-85) years. 256 (71.3%) patients were treated with a minimally invasive approach. There were significantly more female patients (p=0.002) and lower pt-stages (p=0.002) in the VATS group. Nodal upstaging was found in 19.1% in the VATS group and 23.3% in the open group (p=0.486). 5-year disease free survival was 61.2% in the VATS group and 63.8% in the open group (p=0.492). 5-year overall survival was 84.3% in the VATS group and 73.3% in the open group (p=0.139), Figure 1. In a multivariate analysis including age, gender, pt-status, pn-status and surgical approach, none of the factors proved to independently predict disease free survival. In overall survival, a positive pn status was found to be the only independent negative prognostic factor (HR: 2.2, 95% CI: 1.2-4.1).
Conclusion: VATS lobectomy in nodal positive lung cancer patients is oncologically equal to open resection with similar survival and recurrence rates. Half of the lymph node metastases have been missed by clinical staging. Interestingly, the higher rate of patients receiving adjuvant chemotherapy after VATS lobectomy did not result in significant better survival.

Keywords: nodal positive, VATS, thoracotomy

Table 1: Gender, Age, and Smoking Status of Patients

<table>
<thead>
<tr>
<th>Gender</th>
<th>Segmentectomy (n=43)</th>
<th>Lobectomy (n=208)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>21 (49%)</td>
<td>99 (48%)</td>
<td>0.88</td>
</tr>
<tr>
<td>Female</td>
<td>22 (51%)</td>
<td>109 (52%)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>68.4 ± 2.9 (71.8-81.9)</td>
<td>66.4 ± 4.0 (71.8-81.4)</td>
<td>0.27</td>
</tr>
<tr>
<td>BMI</td>
<td>27.2 ± 1.0 (17.4-66)</td>
<td>27.6 ± 1.0 (14.4-52)</td>
<td></td>
</tr>
<tr>
<td>Smoking history (pack-year)</td>
<td>1.06 ± 0.31 (0.9)</td>
<td>1.01 ± 0.30 (0.7)</td>
<td></td>
</tr>
<tr>
<td>Smoking history (years)</td>
<td>43.5 ± 3.1 (7-7)</td>
<td>28.2 ± 1.2 (0-60)</td>
<td>0.48</td>
</tr>
<tr>
<td>Smoking status</td>
<td>50.4 ± 4.5 (9.4-40)</td>
<td>37.5 ± 4.5 (0-40)</td>
<td>0.99</td>
</tr>
</tbody>
</table>

Table 2: Intra-operative complications

<table>
<thead>
<tr>
<th>Intra-operative complication</th>
<th>Segmentectomy (n=42)</th>
<th>Lobectomy (n=208)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothermia</td>
<td>3 (6.9%)</td>
<td>18 (8.6%)</td>
<td>0.70</td>
</tr>
<tr>
<td>Bleeding (PA)</td>
<td>2 (4.7%)</td>
<td>7 (3.4%)</td>
<td>0.71</td>
</tr>
<tr>
<td>Bleeding (PS)</td>
<td>3 (6.9%)</td>
<td>3 (1.4%)</td>
<td>0.085</td>
</tr>
<tr>
<td>Bleeding (other)</td>
<td>12 (2.3%)</td>
<td>10 (4.8%)</td>
<td>0.32</td>
</tr>
<tr>
<td>Phlebitic/Neurolymphg</td>
<td>0 (0.0%)</td>
<td>1 (0.5%)</td>
<td>0.43</td>
</tr>
<tr>
<td>Recurrent/lumensal</td>
<td>0 (0.0%)</td>
<td>2 (0.9%)</td>
<td>0.16</td>
</tr>
<tr>
<td>Nerve injury</td>
<td>0 (0.0%)</td>
<td>3 (1.4%)</td>
<td>0.003</td>
</tr>
<tr>
<td>Fractured/Broken Bone Injury</td>
<td>0 (0.0%)</td>
<td>3 (1.4%)</td>
<td>0.003</td>
</tr>
<tr>
<td>Displacemnt Injury</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Instrumente-related Conversion</td>
<td>0 (0.0%)</td>
<td>20 (9.6%)</td>
<td>0.46</td>
</tr>
</tbody>
</table>

Table 3: Post-Operative Outcomes and Mortality

<table>
<thead>
<tr>
<th>Post-operative outcomes</th>
<th>Segmentectomy (n=43)</th>
<th>Lobectomy (n=208)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1 (ml)</td>
<td>175 ± 34 (120-250)</td>
<td>182 ± 35 (120-250)</td>
<td>0.69</td>
</tr>
<tr>
<td>Pleural effusion (ml)</td>
<td>12 (28.0%)</td>
<td>18 (8.6%)</td>
<td>0.019</td>
</tr>
<tr>
<td>Total hospital stay (d)</td>
<td>5 (2-10)</td>
<td>7 (3-10)</td>
<td>0.003</td>
</tr>
<tr>
<td>Chest tube drainage (ml)</td>
<td>50 (20-100)</td>
<td>100 (20-100)</td>
<td>0.003</td>
</tr>
<tr>
<td>Lymphoma rejection</td>
<td>1 (3.0%)</td>
<td>0 (0.0%)</td>
<td>0.21</td>
</tr>
<tr>
<td>In Hospital mortality</td>
<td>3 (8.9%)</td>
<td>3 (4.4%)</td>
<td>0.73</td>
</tr>
</tbody>
</table>

Table 4: Post-operative complications

<table>
<thead>
<tr>
<th>Post-operative complication</th>
<th>Segmentectomy (n=43)</th>
<th>Lobectomy (n=208)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia</td>
<td>6 (23.2%)</td>
<td>4 (1.4%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Pulmonary edema and www/SDQ complications</td>
<td>9 (38.4%)</td>
<td>31 (18.9%)</td>
<td>0.19</td>
</tr>
<tr>
<td>Aspiration</td>
<td>1 (2.2%)</td>
<td>6 (2.9%)</td>
<td>0.22</td>
</tr>
<tr>
<td>Effort dyspnoea</td>
<td>7 (31.3%)</td>
<td>5 (2.9%)</td>
<td>0.013</td>
</tr>
<tr>
<td>Strokes</td>
<td>7 (31.3%)</td>
<td>7 (3.4%)</td>
<td>0.041</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>3 (8.9%)</td>
<td>0 (0.0%)</td>
<td>0.31</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>2 (5.1%)</td>
<td>3 (1.4%)</td>
<td>0.16</td>
</tr>
<tr>
<td>Sepsis</td>
<td>3 (7.0%)</td>
<td>3 (1.4%)</td>
<td>0.27</td>
</tr>
<tr>
<td>Postoperative complications</td>
<td>6 (23.2%)</td>
<td>4 (1.4%)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Table 5: Number of complications

<table>
<thead>
<tr>
<th>Number (Percent) of complications</th>
<th>Segmentectomy (n=43)</th>
<th>Lobectomy (n=208)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>42 (97.7%)</td>
<td>197 (95.5%)</td>
<td>0.017</td>
</tr>
</tbody>
</table>

Table 6: Median ± SEM (range)

| Median ± SEM (range) |
|-----------------------|----------------------|
| Number (Percent) of complications recorded | 42 (97.7%) | 197 (95.5%) | 0.017 |
No significant difference was found on intra-operative complications (18/208 vs. 4/43; p=0.70). However, the mean duration of R-VATS segmentectomy was longer than lobectomy (258 min vs. 207.5 min; p<0.01). Total post-operative complications didn’t differ between the groups (24/43 vs. 84/208; p=0.071). Individual complications reviewed included cardiovascular, wound infections, and respiratory adverse outcomes. Only pneumothorax after chest tube removal (p=0.032) and effusion/empyema (p=0.011) requiring intervention were significant. Conclusion: R-VATS segmentectomy on average take longer and has more postoperative complications which can be explained by patients’ underlying pulmonary disease. R-VATS segmentectomy may be considered as an alternative procedure to R-VATS lobectomy in order to conserve lung function.

Keywords: segmentectomy, Robotic surgery, complications, lobectomy and metastasectomy.

POSTER SESSION | P1.08 | SURGERY
MINIMAL INVASIVE SURGERY – MONDAY, DECEMBER 5, 2016

P1.08-045 PARTIAL LUNG RESECTION AFTER BRONCHOSCOPIC METALLIC COIL MARKING USING TWO COINS AND CARVED SHAPED FLUOROSCOPIC GUIDANCE
Koh Uyama, Takanori Miyoshi, Hiroyuki Sumitomo, Naoki Hino
Department of Thoracic Surgery, Tokushima Municipal Hospital, Tokushima City/ Japan

Background: The opportunities detecting small pulmonary lesions are increasing because of the spread of CT screening, however, it is sometimes hard to localize the non-palpable tumors located in deep part of the lungs or showing grand-gap opacity lesions. Therefore, it is necessary to mark the location of these tumors before operation. We developed the simple and easy marking technique using two coins and a metallic coil, and examined its reliability, safety, and usefulness. Methods: 23 patients with 24 small peripheral pulmonary lesions less than 20 mm in size underwent fluoroscopy-assisted thorascopic partial lung resection after bronchoscopic metallic coil marking using two coins and C-shaped fluoroscopic guidance. The average diameter of the lesions was 10.33 mm, and the average distance from the pleural surface was 8.37 mm. At first we conducted chest CT scan and confirmed the number of the CT slice in which the tumor exist. Two coins were put on the patient’s chest wall according with the slice number of the antecedent CT scan. A metallic coil was installed in the bronchus near the lesion where the shadows of two coins overlap using ultrathin bronchoscope under C-shaped fluoroscopic guidance. Afterwards, we performed wide wedge resection of the nodules with coil marking under fluoroscopic and thorascopic guidance. Results: We could install coils in the objective bronchi in all cases. The marking procedure took 13 to 39 minutes from insertion to removal of the bronchoscope. There were no complications from the marking, and all 24 nodules were easily localized at the time of VATS resection. The pathologic diagnosis was primary adenocarcinoma in 9 nodules, pulmonary metastases in 8 nodules, a primary squamous carcinoma in 2 nodules, small cell carcinoma in 2 nodules, an atypical adenomatous hyperplasia in 1 nodule, and a nontuberculous mycobacteriosis in 1 nodule. Conclusion: The fluoroscopy-guided coil marking using ultrathin bronchoscope with two coins on a patient’s chest wall after CT-assisted stimulation was a safe, convenient, and reliable method for localization of small pulmonary lesions before VATS partial resection.

Keywords: VATS, coil marking, partial lung resection

POSTER SESSION | P1.08 | SURGERY
MINIMAL INVASIVE SURGERY – MONDAY, DECEMBER 5, 2016

P1.08-046 SURVIVAL FOLLOWING THORACOSCOPIC PULMONARY METASTASECTOMY FOR OSTEOSARCOMA
Takashi Tojo, Takeshi Kagawuchi, Motoaki Yasukawa, Norikazu Kawai, Shigeki Taniguchi
Thoracic and Cardiovascular Surgery, Nara Medical University, Kashihara/Japan

Background: Osteosarcoma is the malignant primary bone tumors which often develop in young people, 5-year overall survival in patients with pulmonary metastasis is around 50%. The objective of this study was to report the overall survival in a group of patients with metastatic osteosarcoma treated with surgical removal of the lung metastases. Methods: A retrospective review from our data base revealed 9 patients performing 18 pulmonary metastasectomies between August 2005 and May 2016. The mean age was 18 years (range, 15-24) and 5 patients were male. All patients were treated with chemotherapy and oncoplastic resection of the primary tumor and thoracoscopic surgical removal of the lung metastases. 4 patients had bilateral lung operations, and only one lung metastasis was resected in three cases and the median number of metastases resected was 1.54. Results: The median overall survival was 34.9 months (range, 7-120). At follow up, 4 patients were dead with a median follow-up of 21.9 months. 5 patients were alive, and 4 patients were disease-free survivors, and 2 of 4 patients had only one pulmonary metastasis at the first lung metastasectomy. Conclusion: In selected patients, thoracoscopically pulmonary metastasectomy for osteosarcoma is safe, and may confer a good survival. Recurrent metastasis after resection confers a good prognosis.

Keywords: osteosarcoma, VATS, pulmonary metastasis, Surgery

POSTER SESSION | P1.08 | SURGERY
MINIMAL INVASIVE SURGERY – MONDAY, DECEMBER 5, 2016

P1.08-047 DECREASING USE OF EPIDURAL ANALGESIA WITH INCREASING MINIMALLY INVASIVE LOBECTOMY: IMPACT ON POSTOPERATIVE MORBIDITY
Mysha Zeltzman, Alexandra Poch, Takashi Eguchi, Sarina Bains, Bernard Park, David Jones, Prasad Adusumili
Thoracic Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York/United States of America

Background: The goal of this study is to assess the impact of the decreasing use of epidural analgesia (infusion ≥24 hours) on the incidence of postoperative morbidity following minimally invasive surgical (MIS; includes VATS and robot-assisted) lobectomy in patients with non-small cell lung cancer (NSCLC). Methods: We reviewed 1206 patients who underwent MIS lobectomy for pathological stage I-III NSCLC in 2009-10 (n=506) and 2014-15 (n=700) at our institution. Clinical data was obtained from a prospectively maintained database and by review of individual patient medical records. Patients with induction therapy (n=225) or conversion from MIS to thoracotomy (n=39) were excluded. Postoperative morbidity (≤30 days) was graded based on the Common Terminology Criteria for Adverse Events (CTCAE). Statistical comparison was performed using Chi-squared analysis and Fisher’s exact test. Results: A total of 884 patients were included in this study (2009-10, n=401; 2014-15, n=483). The rate of MIS lobectomy significantly increased in 2014-15 compared to 2009-10 (74% vs. 53%, p<0.001) with a simultaneous decrease in the use of epidural analgesia (92.9% vs. 53.6%, p<0.001; Figure 1A and 1B). In the MIS group, there was no difference in age, sex, or pathological stage between the 2009-10 and 2014-15 cohorts. There was no significant change in the incidence of any, severe respiratory or cardiovascular morbidity (CTCAE grade ≥2) following MIS lobectomy between the two time periods evaluated (Figure 1C). However, the incidence of CTCAE grade ≥2 respiratory morbidity in 2014-15 was higher than that in 2009-10 (7.1% vs. 12.6%, p=0.047).

Keywords: osteosarcoma, VATS, pulmonary metastasis, Surgery

POSTER SESSION | P1.08 | SURGERY
MINIMAL INVASIVE SURGERY – MONDAY, DECEMBER 5, 2016

P1.08-048 DECREASING USE OF EPIDURAL ANALGESIA WITH INCREASING MINIMALLY INVASIVE LOBECTOMY: IMPACT ON POSTOPERATIVE MORBIDITY

MONDAY, DECEMBER 5, 2016

MINIMAL INVASIVE SURGERY – 

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S395
P1.08-048 COMPARISON OF PULMONARY FUNCTION AFTER ROBOTIC-ASSISTED VIDEO-THORACOSCOPIC LOBECTOMIES VS SEGMENTECTOMIES

Maria Echavarria, Anna Cheng, Frank Velez, Emily Ng, Carla Moodie, Joseph Garrett, Jacques-Pierre Fontaine, Eric Toloza

1University of South Florida, Tampa/FL/United States of America, 2Thoracic Oncology, Moffitt Cancer Center, Tampa/United States of America

Background: Lobectomy is the standard surgical procedure for early stage lung cancer, but sub-lobar resection is being debated. We compared pulmonary function after robotic-assisted video-assisted Thorascopic surgery (R-VATS) lobectomy vs segmentectomy.

Methods: A retrospective analysis of prospectively collected data from 251 consecutive patients who underwent lobectomy (N=208) and segmentectomy (N=43) via R-VATS by one surgeon. Unpaired Student’s t-test and chi-square tests were used to determine statistical significance (p<0.05). Majority of patients had no prior lung surgery. We used “Predicted(PFT)=Preop(PFT)x[(1-Segments x 0.0556)]”, where 0.0556=1seg/18seg. For patients with prior resections, the number of segments previously resected was taken into account(1seg/18-Prior resection).

Table 3: Pulmonary Function Tests

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Segments (n=43)</th>
<th>Lobectomy (n=208)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-op FEV1(L)</td>
<td>2.30±0.41 (0.34-4.42)</td>
<td>2.32±0.05 (0.34-4.48)</td>
<td>0.981</td>
</tr>
<tr>
<td>Pre-op FEV1 (%)</td>
<td>79.4±5.6 (55-122)</td>
<td>82.5±4.7 (35-138)</td>
<td>0.024</td>
</tr>
<tr>
<td>Pre-op DLCO</td>
<td>13.3±9.9 (0.36-34.3)</td>
<td>17.3±6.0 (4.4-32)</td>
<td>0.061</td>
</tr>
<tr>
<td>Pre-op DLCO (%)</td>
<td>61±32.9 (5.0-120)</td>
<td>64.6±14 (14-131)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

Mean ± SEM (range)

Table 4: Predicted Post-Operative Lung Function and Change from Pre-Operative Lung Function

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Segments (n=43)</th>
<th>Lobectomy (n=208)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pred Post-op FEV1</td>
<td>1.9±0.2 (0.81-4.17)</td>
<td>1.8±0.4 (0.87-3.61)</td>
<td>0.65</td>
</tr>
<tr>
<td>Pred Change from Preop FEV1</td>
<td>0.1±0.01 (0.01-0.57)</td>
<td>0.1±0.02 (0.07-1.44)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pred Post-op FEV1 (%)</td>
<td>69±8.1 (33-118.1)</td>
<td>67±4.2 (14.4-112.5)</td>
<td>0.58</td>
</tr>
<tr>
<td>Pred Change from Preop FEV1 (%)</td>
<td>8.5±3.7 (8.5-22.2)</td>
<td>20.6±9.0 (13.1-49.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pred Post-op DLCO (ml/min/mmHg)*</td>
<td>11±0.9 (5.5-21.9)</td>
<td>15±2.0 (4.4-25.6)</td>
<td>0.69</td>
</tr>
<tr>
<td>Pred Change from Preop DLCO (ml/min/mmHg)*</td>
<td>1.3±0.1 (0.44-2.15)</td>
<td>2.6±0.1 (0.65-9.05)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pred Post-op DLCO (%)*</td>
<td>59±8.2 (27.7-113.3)</td>
<td>38±4.1 (20.9-103.49)</td>
<td>0.87</td>
</tr>
<tr>
<td>Pred Change from Preop DLCO (%)*</td>
<td>3.9±0.7 (5.5-22.2)</td>
<td>20±0.8 (11.1-40.8)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Mean ± SEM (range)

Preoperative FEV1(%) and DLCO(%) were statistically significant between the two groups. Also, FEV1 and DLCO were lower in segmentectomy patients. As expected, predicted changes between preoperative and postoperative values were significant. Predicted post-operative FEV1 and DLCO did not show any significant difference between the two groups. Conclusion: While pre-operative PFTs were significantly lower in segmentectomy patients compared to lobectomy patients, predicted post-operative PFTs do not differ significantly. Predicted changes for FEV1 and DLCO are significantly less in segmentectomy. Thus, negate the difference in pre-operative PFTs. In conclusion, R-VATS segmentectomy preserves lung function and may be considered a viable alternative.

Keywords: Robotic surgery lobectomy segmentectomy

P1.08-049 CT GUIDED LABELING WITH INDOCYANINE GREEN OF SMALL LUNG NODULES FOR SUBLOBAR RESECTION UTILIZING ROBOTIC-ASSISTED THORACOSCOPIC SURGERY (RATS)

K Adam Lee,1 Lee Fox,2 Andrew Hall,1 Vincent Turiano2

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Background: Localization of deep and small pulmonary lung nodules undergoing a wedge or sublobar resection may be challenging during thoracoscopic, and may necessitate greater resection or conversion to thoracotomy. Particularly in robotic surgery, with the absence of tactile feedback. Percutaneous CT guided Indocyanine Green injection provides a means to pinpoint these nodules. Methods: A retrospective study of 40 consecutive patients who underwent preoperative CT-guided localization of solitary pulmonary nodules with ICG. Nodules ≤ 15mm were 21/40 (52.5%), >15mm ≤ 20mm 30/40 (75%), and >20mm 30/40 (95%). A 22-gauge spinal needle (BD, NJ) or Chiba needle (Cook, IA) was positioned into or adjacent to the nodule. 0.4cc Indocyanine Green was injected and the inner stylet withdrawn. The Xe daVinci robot (Intuitive Surgery, CA) was docked and the firefly filter of the 8mm camera was activated, and the nodule illuminates in a florescent green color. A wedge or sublobar resection was performed, with progression to lobectomy when indicated. Results: CT guidance successfully localized the nodules in 100% of 40 patients employing this technique. Success was measured in nodule illumination as seen by the surgeon upon activation of the camera filter and confirmed on frozen and permanent section by pathology. Initial wedge resection for diagnosis prior to lobectomy and sublobar resection for decreased PFTs or decrease cardiac function were performed by Robotic Assisted Thorascopic surgery (RATS). There were no conversions to thoracotomy. Diagnosis were adenocarcinoma in 18 patients (45%), squamous cell carcinoma in 7 patients (17.5%), carcinoid in 1 patient (2.5%), metastatic in 8 patients (20%), and benign in 6 patients (15%). There were no 30 or 90 day mortalities. A chest tube reinsertion in one patient for pneumothorax. Economically the cost for the vial of ICG is $79.56 compared to a fiducial marker at a cost of $128.00. Thoracic Surgery has access to CT scanners, without an extra cost, electromagnetic navigation systems come with significant added costs. Conclusion: Percutaneous CT guided labeling with ICG is quick and economical for the localization of small and deep nodules undergoing RATS wedge or sublobar resection. This technique may be supportive in preserving lung parenchyma and reduce the need for conversion to thoracotomy, maintaining minimal invasive thoracic surgery, especially where palpation or tactile feedback is absent.

Keywords: pulmonary nodules, sublobar resection, Minimal Invasive thoracic surgery, CT guided labeling
the intraoperative blood loss and didn’t imply a significant impact in terms of intraoperative conversion to open surgery. We detected differences in the operation length and in chest drain maintenance. Other studies with an higher population of “complex cases” are needed, but we are trustful that VATS lobectomy indications will be extended in the short term.

Keywords: lobectomy, NSCLC, VATS, sleeve

P1.08-051 VATS LOBECTOMY COMBINED WITH LIMITED THORACOTOMY FOR TREATMENT OF SUPERIOR SULCUS TUMORS

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Background: Despite the increasing of VATS procedures even for locally advanced NSCLC, Pancoast tumors have been rarely approached with VATS combined with chest wall resection. This report describes an hybrid surgical technique to approach “en block” chest resection and pulmonary lobectomy for superior sulcus tumors: Methods: We present 2 cases of patients referred to our Institution. A female patient affected by right anterior Pancoast tumor surgically staged as cT4N0M0 for suspected anomalous vein invasion, underwent induction therapy with four cycles of cisplatin and Pemetrexed plus 60 Gy irradiation, with satisfactory tumor reduction. The surgical operation comprised an initial VATS approach to the hilar structures followed by a limited C-shaped anterior coni-cision; finally, the right upper lobe “en block” with the anterior part of the first and second rib was removed. The second case is a 57-year-old man, affected by a cT3N0M0 posterior Pancoast tumor, treated with indium prior to the hybrid surgical approach. After thoracoscopic pleural cavity inspection, an upper right VATS lobectomy by a 3-port standard approach was performed. The chest wall was resected through a limited paravertebral incision, allowing the extraction of the lobe together with the rib segments. The posterior chest wall defect was repaired with a synthetic patch. Results: The postoperative period was uneventful in both cases, and the pain never exceed a score of 4 on a visual analogue scale. The patients were discharged respectively 9 and 11 days after surgery. Pathological results revealed in both cases nonivtal tumor cells in the specimen (ypT0N0M0). The patients are free from disease recurrence and post-thoracotomy syndrome at 14 and 18 months’ follow-up Conclusion: VATS combined with thoracotomy approach leads to assess with precision the tumor cells in the specimen (ypT0N0M0). The patients are free from disease recurrence and post-thoracotomy syndrome at 14 and 18 months’ follow-up Conclusion: VATS lobectomy represents the pinnacle of evolution for minimally invasive surgery. VATS offers the advantage of minimizing the extent of the surgical access trauma thus resulting in lower morbidity and shorter hospital stay compared to thoracotomy. VATS can be considered as a safe and effective hybrid approach in selected cases. VATS lobectomy is an oncologically complete procedure with better clinical outcomes and postoperative complications than thoracotomy.

Keywords: VATS, Surgery, Pancoast

P1.08-052 COMPARISON STUDY OF PERIOPERATIVE OUTCOMES IN ROBOTIC, VIDEO-ASSISTED THORACIC SURGERY, AND THORACOTOMY APPROACHES FOR LUNG CANCER

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Background: Robotic surgery for lung cancer has not widely spread because of the lack of definitive advantage compared to conventional approaches, specifically video-assisted thoracic surgery (VATS). Some studies have reported that postoperative complication in robotic surgery is superior for unclear reasons. The aim of this study is to compare the perioperative outcomes, particularly pointing out postoperative complication among robotic, video-assisted thoracic surgery (VATS) and thoracotomy approach in non-small cell lung cancer (NSCLC). Methods: We performed a retrospective review of NSCLC patients who underwent curative anatomical resection in our hospital from January 2011 to April 2016. There were 346 lobectomy cases and 76 segmentectomy cases. The patients were classified into four groups (robotic, VATS, open conversion from VATS, and thoracotomy) and were compared for differences in perioperative outcomes. Results: Total 422 patients (43 robotic, 265 VATS, 30 open conversion from VATS, and 84 thoracotomy) were included in the analysis. Clinical and pathological stage showed earlier in robotic and VATS cases. Operative time (min), bleeding amount (gram) and drainage period (days) for robot, VATS, conversion and thoracotomy were 247/20/2, 188/10/2, 246/100/2, 225/92/5 respectively (p<0.0001). In the incidence of all, over G3, respiratory over G3 postoperative complications robotic surgery showed significantly lowest among them and there were neither conversion to thoracotomy nor postoperative/hospital mortality in robotic surgery. Conclusion: In our initial results of robotic surgery, lower incidence of operative morbidities is one of the advantageous features. Important issue whether robotic surgery is established as a minimally invasive approach for NSCLC or not should be verified.

Keywords: NSCLC, thoracotomy, Robotic surgery, VATS

P1.08-053 THORACOSCOPIC PARTIAL RESECTION FOR PERIPHERAL PULMONARY NODULES WITHOUT USING STAPLER

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Background: Advances in radiologic studies, such as high resolution computed tomography (HRCT), have enabled frequent detection of small lung nodules. Accordingly, opportunity for sublobar resections for small lesions has increased. Recently, we have introduced thoracoscopic partial resection for peripheral pulmonary small nodules without using stapler to reduce the cost of operation. Methods: After detecting the peripheral nodules, partial resection was performed with electrocautery and two different methods of surface sealing were followed. Coagulation method (C method) with SOFT COAG alone and Coagulation-suturing method (CS method) with SOFT COAG combined with continuous suturing by an absorbable barbed suture. The clinical outcome of the two methods was retrospectively compared in this study. Results: C method was performed in 19 lesions of 18 cases and CS method was performed in 17 lesions of 16 cases. Primary lung cancer was most frequent as 19 lesions of 18 cases. There was no significant difference between the two groups in size and depth of the lesions. Operation time was significantly longer in C method than in CS method. Postoperative air leakage was complicated to 4 cases in C method and one of them needed re-do surgery, whereas only one case in CS method had temporary air leakage. Postoperative computed tomography revealed cavitation in 3 cases of C method and in 4 cases of CS method all without related symptoms. There was no local recurrence in restected sites. Conclusion: C method was technically easy to perform, but air leakage may be possibly prolonged after surgery. CS method may have an advantage of less air leakage than C method, but technical learning is important to shorten operation time.

Keywords: partial lung resection, SOFT COAG, continuous suturing, Thoracoscopic surgery

P1.08-054 UNIPORTAL VATS LOBECTOMY IN THE TREATMENT OF NSCLC

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Background: Uniporal Video-Assisted Thoracic Surgery (uniporal VATS) lobectomy represents the pinnacle of evolution for minimally invasive techniques in surgical management of lung cancer. Growing evidence suggest that Uniporal VATS procedures are technically feasible and safe with immediate outcomes comparable to traditional VATS approach. Uniporal approach has demonstrated equivalent disease-free survival, at intermediate follow-up for patients with early stage NSCLC, compared to conventional VATS. It represents a less invasive approach, and offers the advantage of minimizing the extent of the surgical access trauma thus resulting in postoperative pain reduction, muffled inflammatory response, early recovery and better cosmesis. Some authors described minimal changes in pulmonary function after uniporal surgery in patients with poor cardio-respiratory function. Here we present our experiences with uniportal VATS lobectomies
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for NSCLC. Methods: Between October 2015 and March 2016, twenty-four (24) patients with non-small lung cancer (NSCLC) underwent unipolar VATS lobectomy and mediastinal lymph node dissection. Surgical access was performed through a 4-5 cm long utilitarian incision at the 5th intercostal space in the anterior axillary line. Anatomical resection of veins, arteries, bronchi and mediastinal lymph nodes followed established anatomical principals. Once the operation was completed a single chest tube was inserted in the anterior part of the incision for unipolar VATS. Results: Fifteen male and nine female patients with an average age of 62.6 years (49-76) were enrolled in the study. Average procedural time was 108 minutes (75min-154min). None of the patients required blood transfusion after the procedure or during the rest of their hospital stay. Average duration of chest drainage was 3.6 days (2-8) and mean hospital stay was 6 days (3-10). There were 14 patients with adenocarcinoma and 10 with squamous cell carcinoma. Two patients had prolonged air leak and were treated conservatively. There was no perioperative mortality. Conclusion: Our initial experiences with Unipolar VATS lobectomy is encouraging as it demonstrated benefits to patients due minimal surgical stress, faster recovery, reduced postoperative pain and shorter hospital stay.

Keywords: VATS, unipolar, NSCLC

P01.08-055 HAND ASSISTED THORACOSCOPIC SURGERY (HATS) FOR METASTATIC LUNG TUMORS - IMPROVED TECHNIQUE FOR MORE SAFETY AND ACCURACY
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Background: Small pulmonary lesions, the localization of which cannot be confirmed by the sight, are often removed surgically with help of several type markers. But they sometimes drop off or dislocate before surgery. It is the most certain to confirm local existence of tumors with help of palpation and remove them surgically. I reported the usefulness of hand assisted thoracoscopic surgery (HATS) for such cases. We removed about 15% more lesions than the number that we expected before surgery using this technique. Methods: A hand of surgeon was inserted into the bilateral thoracic cavities of patients through a subxiphoid skin incision in supine position in the method of original HATS. Results: HATS is relative safe and useful technique. But there is only one problem in this technique. Surgeon can palpate whole lungs from the pulmonary apex to a base of lung in right side without circulatory complication. But, in left side, blood pressure sometimes decreases by a surgeon’s arm pressing left ventricle. In such a case, we change patients’ position from supine to left side up. Circulatory complications decreases in this improved technique. Conclusion: HATS in supine position for right side and in left side up position for left side is safer and more accurate method. Improved data got with improved technique will present on the poster of congress.

Keywords: hand-assisted, small lesion, palpation, circulatory complication

P01.08-056 SURGICAL RESULTS OF THORACOSCOPIC ANATOMICAL SUBLOBAR RESECTIONS FOR EARLY-LATE STAGE LUNG CANCER
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Background: High-resolution computed tomography (HRCT) has been used to detect ground glass nodules (GGN), and sublobar resections might be currently accepted for patients with early stage malignant GGN. Aim of this study was to evaluate the surgical results of thoracoscopic sublobar resections for early-stage lung cancer. Methods: Twenty patients (6 males and 14 females, a mean age of 72.5 years) performed surgical treatment for thoracoscopic anatomical sublobar resections from April 2012 to May 2016. Anatomical sublobar resections were selected with the following criteria: stage Ia disease with no regional lymph node metastasis; tumor up to 2 cm in diameter; a low tumor standardized uptake value (SUVA) evaluated in (18)F-fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET); predominantly ground-glass appearance on CT imaging. The high resolution CT scanner, Philips Brilliance ICT (Medical Imaging Resources, An Arbor, MI) with both 128 and 256 slice configurations was used. CT data were transferred to an imaging analysis system (Zio station ver.2, Tokyo, Japan) for image reconstruction and we performed preoperative CT-guided marking in surface of near the tumor. Results: In all 20 cases, the reconstruction of the pulmonary artery and vein could image branches and resected in lung segment. Right side: One case of the upper lobe S1, 5 cases of the lower lobe S6 (3), S8 (1) and S10 (1). Left side: 10 cases of the upper lobe S1+2a, 2+3c, S1+2a+b, S1c+2a+S3a, S3b+c, apicoposterior segmentectomy, S32 (1) and upper lobe trisegmentectomy (2); 4 cases of the lower lobe S6, S8+S9, S10 and basal segmentectomy. All pulmonary nodules were found in the excised target segments with safety margin. According to postoperative pathological examination of the all operative specimens were adenocarcinoma, and the diameters of pulmonary tumors resected were 15.8±3.3 and invasive size were 6.2±3.1 mm. Furthermore, the pathological results were given Atypical adenomatous hyperplasia (2), adenocarcinoma in situ (2), minimally invasive adenocarcinoma (5), Lepidic predominant adenocarcinoma (10) and papillary predominant adenocarcinoma (1). Conclusion: At the time of writing, local recurrences had not occurred in sublobar resection, so we should be considered for early stage lung cancer in these conditions. Moreover the 3D-CT angioigraphy could be used preoperatively as a tracing method to identify the resected line of lung segment and very useful for anatomic sublobar resections, especially in thoracoscopic surgery.

Keywords: 3D-CT angiography, Early-stage lung cancer, Thoracoscopic surgery, Anatomic sublobar resection
Background: The timing of surgery after induction chemoradiotherapy (ChRT) for locally advanced NSCLC is accepted crucial because of technical difficulties, morbidity and related mortality. Although six to eight weeks’ time interval after induction ChRT and surgery is advocated, precise analysis of the optimal waiting time that maximizes oncologic benefits of ChRT has not been established. We aimed to review our results of pulmonary resections performed after induction ChRT and to determine the effects of time interval on postoperative morbidity, mortality and long term survival. Methods: We retrospectively reviewed our records for patients undergoing induction ChRT between 1996 and 2015. Timing of treatment was defined as the difference between the last date of radiotherapy and the date of lung resection. The dose of radiotherapy varied from 45Gy to 66Gy. The patients were divided into two groups, surgery less than eight weeks (Group 1) and more than eight weeks (Group 2) following induction ChRT. Type of resection, postoperative complications, 90-days mortality and long-term survival were analyzed. The impact of surgical timing on outcomes was studied through univariable and multivariable analyses. Results: One hundred and forty-two patients were included into study. The mean time interval between ChRT and surgery was 92.3 days (21-900 days). Sixty-five lung resections were performed less than eight and 77 more than eight weeks. Pulmonary resections were classified as pneumonectomy in 20 patients, lobectomy in 122 patients (of whom, 55 underwent extended resections, chest wall, sleeve etc.). Final pathological examination revealed complete response in 43 (30.3%) of the patients. Major morbidity was observed in 42.2% of the patients (43% (28 of 65pts) in group 1 and 41.5% (32 of 77pts) in group 2, p=0.85). The overall 90-day mortality rate was 6.3% (7.7% in group 1 and 5.2% in group 2, p=0.54). The mortality rate after pneumonectomy was 5% (1/20) and 6.5% (5/77) after lobectomy. The 5-year survival rate of 6% (4/67) vs 5% (5/77) was not significantly associated with an increased morbidity and mortality that was also not affected by the dose of radiotherapy. Conclusion: These findings indicate that lobectomy or pneumonectomy can be safely performed eight weeks or more after induction ChRT without affecting surgical morbidity and mortality. Pulmonary resection may be performed safely even one year after ChRT.

Keywords: Locally advanced NSCLC, Chemoradiotherapy, Surgery

P01.08-060 SURVIVAL OF PATIENTS WITH UNSUSPECTED N2 (STAGE IIIA) NON-SMALL CELL LUNG CANCER
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Background: There are few studies evaluating the N2 pattern and outcomes when a patient with non–small cell lung cancer (NSCLC) unexpectedly is found to have N2 disease at the time of thoracotomy or thoracoscopy. The objective of this study was to determine the survival of patients who have completely resected, non-small-cell, stage IIIA, lung cancer from unsuspected (nonimaged) N2 disease. Methods: A retrospective review of NSCLC patients treated with surgery was performed. The decision to operate was based on clinical suspicion, and imaging was performed only when indicated. All patients underwent N2 staging before surgery. The N2 pattern was confirmed by extrapulmonary lymphadenectomy during surgery. Multivariable analysis of the optimal waiting time that maximizes oncologic benefits of ChRT has not been established. We aimed to review our results of pulmonary resections performed after induction ChRT and to determine the effects of time interval on postoperative morbidity, mortality and long term survival. Time interval on postoperative morbidity, mortality and long term survival. Results: Unsuspected pN2 disease was found in 10.9% of patients (31 out of 284) who underwent lobectomy as primary therapy for cT1-cT3 cN0-cN1 NSCLC. Of these, cN0pN2 and cN1pN2 were 9.6% (26 out of 270) and 35% (5 out of 14), respectively. Comparing to cN0 group, unsuspected pN2 was more frequent in the cN1group (p=0.003). In terms of the pattern of metastasis, multiple and single pN2 was observed similarly in cN0 and cN1 group (p=0.94). The 5-year overall survival of the entire unsuspected pN2 was 68.5%, and cN0pN2 cohort tended to have better prognosis than cN1pN2 cohort (71.1% vs 50.0%; p=0.089). No significant difference in 5y-OS between unsuspected single and multiple pN2 could be seen (70.3% (single) vs 66.7% (multiple); p=0.7803). Conclusion: This analysis suggests that, in the setting of unsuspected pN2 NSCLC, proceeding with anatomic surgery does not appear to compromise outcomes. As unsuspected pN2 disease was more frequent in cN1 cohort and revealed poor prognosis, perioperative invasive mediastinal staging and additional therapy should be considered.

Keywords: Surgery, postoperative outcome, nodal staging, non-small cell lung cancer
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P1.08-061 CLINICAL EXPERIENCE OF RIB RESECTION FOR LUNG CANCER WITH CHEST WALL INVASION USING A PNEUMATIC HIGH SPEED POWER DRILL SYSTEM

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Background: Rib resection is sometimes required for chest wall tumors or lung cancer with localized chest wall invasion. There are some reports on thoracoscopic rib resection, which may be much less invasive and provide an excellent surgical view of the target. We have used a pneumatic high speed power drill system, commonly used as a dentist’s drill, in order to be accomplished less invasive thoracoscopic rib resection. Methods: A pneumatic high speed power drill (HiLAN® GA520R B Braun Aesculap, Tokyo, Japan) was inserted in the thoracic cavity and the head of the drill, which has a diamond burr, adequately attached to the rib surface. The rib was then sheared by whistling until dislocated. Cut pieces of bone tissue were removed by suction with saline dropping on the head of the drill. Soft tissue including the parietal pleura, intercostal muscle and vessels were dissected using power devices or an electrical scalpel after cutting the ribs.

Results: From February 2014 to date, we have experienced seven patients with chest wall resection using a drill. Hybrid-VATS was performed for four of the patients, while complete-VATS was performed for the remaining three patients. There were no intraoperative issues and the postoperative courses were all eventless. The mean follow-up period is about 13 months. Two of the 7 patients had recurrence of the disease with distant metastasis. However, there is no local recurrence. Conclusion: A pneumatic high speed power drill is easy to handle and useful for rib resection in lung cancer surgery and possibly better suited even when compared to the Gigli saw or endoscopic rib cutter for selective patients undergoing thoracoscopic surgery. Rib resection using a drill might be less invasive procedure.

Keywords: rib resection, drill, Thoracoscopy, chest wall

P1.08-062 THE SHORT AND LONG-TERM OUTCOMES OF COMPLETION PNEUMONECTOMY COMPARED WITH PRIMARY PNEUMONECTOMY

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Background: Completion pneumonectomy has been reported to be high morbidity and mortality procedure in lung cancer patients. However, we sometimes have no choice but to apply this procedure for the patients who developed secondary lung cancer in the remaining lung after lung resection, local recurrence, or postoperative complication. In this study, we investigated the short and long-term outcomes of completion pneumonectomy compared with primary pneumonectomy in our single institution. Methods: Between January 1997 and December 2014, 243 patients who underwent pneumonectomy in our institution were enrolled in this study. Retrospectively, we investigated the postoperative complication, short and long-term outcomes of the patients who underwent completion pneumonectomy (CP) and primary pneumonectomy (PP). CP was defined as pneumonectomy in patients with previous lung resection conducting a hilar manipulation. Results: Thirty-three patients (14%) of 243 patients underwent CP. CP was performed for 28 malignant tumors and 5 benign diseases. Postoperative severe complication (CTCAE Grade 3 or more) occurred in 36% of CP group and 12% of PP group (p<0.01). Especially, bronchopleural fistula (BPF) was more likely to occur in patients undergoing CP (PP 5% vs CP 15%, p=0.03). The incidence of BPF in PP group was related to the side of procedure (right 70% versus left 30%, p<0.01), but those in CP group was not related (right 60% versus left 40%, p=0.57). In the patient with BPF after CP, Bronchial stump coverage was performed in 2 of 5 patients undergoing the right-side procedure, not performed in other 3 of 5 patients (2 left-side and 1 right-side). The 30-day mortality for CP group (9%) was a significantly higher compared with PP group (2%, p=0.04). However, the 90-day mortality (PP 5% vs CP 12%, p=0.14) and the overall survival (PP 47% vs CP 52%, p=0.44) were not significant difference between the two groups. Conclusion: Postoperative morbidity and 30-days mortality rates in CP were higher than those in PP group, but the long-term survival of CP is acceptable compared with PP group. The incidence of left-side BPF is similar to right-side in CP group in this study. It will be also necessary to take preventive procedure against BPF (bronchial stump coverage) in left-side CP.

Keywords: completion pneumonectomy

P1.08-063 DOUBLE PRIMARY MALIGNANCIES INVOLVING LUNG CANCER AND HEPATOCELLULAR CARCINOMA

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Background: The incidence of double primary malignancies (DPM) with lung cancer and hepatocellular carcinoma (HCC) has increased in gradually. However there was a lack of data about the clinical outcomes and factors. We performed a retrospective study to investigate overall survival and characteristics in that patients. Methods: Between January, 2002 and December, 2013, total 52 patients had DPM. 7 patients were excluded because there was lack of medical record. 3 patients with other malignancies were excluded. We divided the patients into 2 groups. 19 patients were synchronous group that interval of diagnosis between 2 malignancies was shorter than 180 days and other 23 patients were metachronous group. Results: Among 42 patients with DPM, there were no significant differences in basic characteristics. Median overall survival was 118.37 ± 6.39 months. There was no significant difference in overall survival between synchronous group and metachronous group (p = 0.921). Multivariate analysis revealed that higher lung cancer stage, postoperative therapy due to lung cancer, liver cirrhosis, and history of hypertension were independent factors for overall survival.

Keywords: double primary malignancies, lung cancer and hepatocellular carcinoma

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The occurrence of postoperative complications was not associated with age, sex, histology, or mode of lung resection. Mortality (0%) and prolonged air leak (2%) did not occur in patients who received pneumonectomy. There was no operative or in-hospital death.

**Conclusion:** Lobectomy with PA-resection and reconstruction was feasible to avoid pneumonectomy for tumor invading proximal left PA.

**Keywords:** lung tumor, Angioplasty, Left main pulmonary artery

**P1.08-064 SURGERY FOR MALIGNANT PULMONARY TUMOR INVADING PROXIMAL LEFT MAIN PULMONARY ARTERY**

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**Background:** Surgery for tumor invading proximal left main pulmonary artery (PA) may be technical challenge, and the current study conducted to assess its feasibility. Methods: Patients who received surgery for malignant pulmonary tumor invading left main PA, PA proximal to the first branch (usually A3), from 2011 through 2015 in our institute were retrospectively reviewed. Results: Among 32 eligible patients (Table 1), 31 (97%) patients received complete resection with pneumonectomy (n=4) or lobectomy with PA-reconstruction (n=27). Pericardiectomy was necessary for proximal control of main PA in 12 patients, and combined bronchial sleeve resection and reconstruction were performed in 11 patients. Postoperative complications occurred in 7 patients, but a > grade 3 complication (ARDS) occurred in only one patient who received pneumonectomy. There was no operative or in-hospital death.

**Table 1. Multivariate survival analysis of prognostic factors in double primary malignancies with lung cancer and HCC**

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<thead>
<tr>
<th>Characteristics</th>
<th>Univariate</th>
<th>Multivariate</th>
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<tbody>
<tr>
<td></td>
<td>p Value</td>
<td>HR (95% CI)</td>
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<td>Lung cancer</td>
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<tr>
<td>Stage (TNM)</td>
<td>0.001</td>
<td>0.63-1.48</td>
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<tr>
<td>I</td>
<td></td>
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<tr>
<td>II</td>
<td>28.77 (2.94-281.91)</td>
<td>0.004</td>
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<tr>
<td>III</td>
<td>578.42 (18.39-18086.41)</td>
<td>0.000</td>
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<tr>
<td>Postoperative therapy</td>
<td>0.023</td>
<td>0.022 (0.006-0.34)</td>
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<tr>
<td>HCC LLC</td>
<td>0.035</td>
<td>3.15 (1.01-9.98)</td>
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<td>History of Hypercemia</td>
<td>0.149</td>
<td>0.16 (0.035-0.679)</td>
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**Conclusion:** Lung cancer stage and underlying liver cirrhosis were strongly related to overall survival in patients with DPM involving lung cancer and HCC. Absence of hypertension showed better prognosis in those patients.

**Keywords:** lung cancer, hepatocellular carcinoma, double primary malignancies

**P1.08-066 SURGERY FOR MALIGNANT PULMONARY TUMOR INVADING PROXIMAL LEFT MAIN PULMONARY ARTERY**

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**Background:** Metastatic non-small cell lung cancer (NSCLC) is an incurable disease. Selected patients with solitary brain metastasis from NSCLC can achieve long-term survival following metastasectomy. We analyzed the outcome of all consecutive and unselected patients undergoing resection of brain metastases in two cancer centers in Switzerland to assess safety and efficacy of brain metastasis resection in NSCLC. Methods: 119 consecutive NSCLC patients undergoing surgical resection of brain metastases from two centers in Switzerland (University Hospital Basel, Cantonal Hospital St. Gallen) between 2000 and 2014 were analyzed. Measured outcomes were extent of resection, resection status, postoperative complications and overall survival (OS). We used the log-rank test to compare unadjusted survival probabilities and multivariable Cox regression potential prognostic factors with respect to OS. Results: Median age was 60.5 years, 56% were male, 74% were smokers, 55% had adenocarcinoma. Median OS of the whole cohort was 18.0 months. 1-year survival rate was 63%, 12% of patients were alive after 5 years. In total, 146 brain metastases were resected; the maximum number of resected metastases was 4 (median 1). Median diameter of resected metastases was 25 millimeters (range, 6.70 mm). About half of metastases were localized in the frontal cortex or the cerebellum. 86% of patients received postoperative radiotherapy. 63% of patients were treated with whole brain radiation, 12.6% received stereotactic radiotherapy. Median dose of postoperative radiotherapy was 30 Gy. Patients not receiving adjuvant radiotherapy (n=11) had a significantly worse outcome (median OS 9.0 vs. 20.2 months, p=0.002). Patients with more than one brain metastasis (n=21) had a significantly worse outcome compared to those with a solitary metastasis (median OS 13.5 vs. 19.5 months, p=0.006). Also patients with extracerebral metastases (n=33) had a significantly poorer outcome (median OS 14.0 vs. 23.1 months, p=0.005). Patients with non-squamous histology (n=98) had a better outcome than patients with squamous cell carcinoma (median OS 22.6 vs. 12.0 months, p=0.019). 21% of patients experienced postoperative complications, including need for surgical reintervention (5.8%), neurological deficits (4.2%), infection (4.2%), stroke (3.4%) and others (11.8%). The occurrence of postoperative complications was not associated with outcome. In the multivariate analysis existence of extracerebral metastases and resection of more than one brain metastasis were independent negative prognostic factors. Conclusion: Patients with isolated brain metastasis from NSCLC in the absence of extracranial metastasis should be evaluated for metastasectomy. Prospective trials are needed to characterize the patient population experiencing the greatest benefit from a surgical procedure.

**Keywords:** Brain metastasis, metastasectomy, Radiotherapy, Prognosis

**P1.08-065 PROGNOSTIC FACTORS OF POST-RECURRENCE SURVIVAL IN PATIENTS WITH COMPLETELY RESECTED STAGE III-N2 NON-SMALL CELL LUNG CANCER**

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**Background:** Survival rates for locally advanced and advanced NSCLC have improved considerably in recent years. Early and adjuvant resection of brain metastases in two cancer centers in Switzerland to assess safety and efficacy of brain metastasis resection in NSCLC. Methods: 119 consecutive NSCLC patients undergoing surgical resection of brain metastases from two centers in Switzerland (University Hospital Basel, Cantonal Hospital St. Gallen) between 2000 and 2014 were analyzed. Measured outcomes were extent of resection, resection status, postoperative complications and overall survival (OS). We used the log-rank test to compare unadjusted survival probabilities and multivariable Cox regression potential prognostic factors with respect to OS. Results: Median age was 60.5 years, 56% were male, 74% were smokers, 55% had adenocarcinoma. Median OS of the whole cohort was 18.0 months. 1-year survival rate was 63%, 12% of patients were alive after 5 years. In total, 146 brain metastases were resected; the maximum number of resected metastases was 4 (median 1). Median diameter of resected metastases was 25 millimeters (range, 6.70 mm). About half of metastases were localized in the frontal cortex or the cerebellum. 86% of patients received postoperative radiotherapy. 63% of patients were treated with whole brain radiation, 12.6% received stereotactic radiotherapy. Median dose of postoperative radiotherapy was 30 Gy. Patients not receiving adjuvant radiotherapy (n=11) had a significantly worse outcome (median OS 9.0 vs. 20.2 months, p=0.002). Patients with more than one brain metastasis (n=21) had a significantly worse outcome compared to those with a solitary metastasis (median OS 13.5 vs. 19.5 months, p=0.006). Also patients with extracerebral metastases (n=33) had a significantly poorer outcome (median OS 14.0 vs. 23.1 months, p=0.005). Patients with non-squamous histology (n=98) had a better outcome than patients with squamous cell carcinoma (median OS 22.6 vs. 12.0 months, p=0.019). 21% of patients experienced postoperative complications, including need for surgical reintervention (5.8%), neurological deficits (4.2%), infection (4.2%), stroke (3.4%) and others (11.8%). The occurrence of postoperative complications was not associated with outcome. In the multivariate analysis existence of extracerebral metastases and resection of more than one brain metastasis were independent negative prognostic factors. Conclusion: Patients with isolated brain metastasis from NSCLC in the absence of extracranial metastasis should be evaluated for metastasectomy. Prospective trials are needed to characterize the patient population experiencing the greatest benefit from a surgical procedure.

**Keywords:** Brain metastasis, metastasectomy, Radiotherapy, Prognosis

**P1.08-066 SURGERY FOR LOCALLY ADVANCED AND ADVANCED NSCLC – POSTER SESSION 1, MONDAY, DECEMBER 5, 2016**

**S401**
was no significant difference in occurrence of post-operative complication. Conclusion: Ipsilateral surgery, especially completion pneumonectomy for 2nd primary lung cancer was more difficult procedure. However, ipsilateral and contralateral surgery was equivalent in feasibility. Contralateral 2nd primary lung cancer is indication for surgery. However, second surgery for ipsilateral 2nd primary lung cancer requires careful consideration.

**P1.08-068 SALVAGE SURGICAL RESSECTION AFTER CURATIVE-INTENT CONCURRENT CHEMORADIOTHERAPY FOR N2-STAGE III LUNG CANCER**

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Background: A concurrent chemoradiotherapy (CRT) is thought to be the curative treatment for N2 Stage IIIA locally advanced lung cancer (LALC). However, after the CRT the cancer sometimes remained the treatment field. The radical pulmonary resection of residual cancer after CRT is one of the option for the treatment. Methods: We retrospectively evaluated 20 patients who received curative-intent CRT and radical surgical resection for LALC from January 2003 to April 2016. The initial treatment for LALC consisted of platinum based 2 drugs with concurrent curative thoracic radiotherapy (60Gy). Results: The mean age at the surgery was 62.8 years (range 46–80 years), two women and 18 men. The mean interval from CRT to the surgery was 25 months (range 3-96 months). All patients except two cases underwent complete surgical resection with mediastinal nodal dissection including lobectomy in 15 cases, lobectomy with bronchoplasty in 2 cases, pneumonectomy in 2 cases and 1 wedge resection. The bronchial stump was covered with pericardial fat tissue or intercostal muscle. Histological type was adenocarcinoma in 11 cases, squamous carcinoma in 6 cases, large-cell carcinoma in 2 cases, and combined cell type small-cell carcinoma in one case. The mean operation time was 320 minutes (range 163-649 minutes), and mean blood loss was 868g (range 90-6000g). There was no operative mortality and 8 cases post-operative morbidity such as arrhythmia in 4 cases, atelectasis in 2 cases, pneumonia, ileus and heart failure in each. There was no bronchopleural fistula or bronchial dehiscence. The 3 and 5 years survival after surgical resection was 70% and 43% with 63 months median follow-up period. Conclusion: The radical pulmonary resection after curative-intent concurrent chemoradiotherapy is feasible with careful patient selection, operative procedure and meticulous perioperative care.

Keywords: trimodality treatment, salvage surgery, Stage III locally advanced lung cancer, Curative treatment.

**P1.08-069 ONE SURGEON’S 30-YEAR EXPERIENCE OF SURGICAL TREATMENT FOR PANCOAST TUMOR**

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Background: Surgical treatment for Pancoast tumor has made marked progress, and the patient outcome has improved significantly over the last three decades. Developments of some new surgical approaches and the application of preoperative chemo-radiotherapy markedly contributed. Methods: We retrospectively analyzed the patients who received surgical treatment in two institutes between 1986 and 2013. One surgeon planned the surgical treatment and performed the operation in all patients. Results: Seventy-two patients received surgical treatment. There were 61 males and 11 females; with median age of 61 years old (33-83 years). There were 26 adenocarcinomas, 26 squamous cell carcinomas, 10 large cell carcinomas, and 10 other pathologies. Forty patients received preoperative induction therapy. Twenty-five patients were treated by induction chemo-radiotherapy with a platinum doublet and 50-55Gy of concurrent radiotherapy. Fourteen patients received radiotherapy alone, and another one patient received chemotherapy alone. The surgical approach was selected based on the tumor location. An anterior approach including Masaoka’s approach, Dartevele’s approach, and Grunenwald’s approach were adopted for 19 patients. Posterior approach, all involving a hook approach was employed in 52 patients. One patient was operated on using both anterior and posterior approaches. Combined resection excluding the chest wall was performed in 59 patients. The brachial...
Keywords: surgical approach, lung cancer, Pancoast tumor, induction chemotherapy-radiotherapy

P1.08-070 SALVAGE LUNG SURGERY: DIFFICULTIES AND RESULTS
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Background: Thoracic surgeons often encounter lung resections following neoadjuvant treatments. Despite that, sometimes patients have curative chemotherapies and radiotherapy treatments according to various factors at the time of diagnosis. After these treatments, the possibility of recurrence increases. When a patient has developed a recurrence, the decision for surgery could be difficult. The aim of this study was to assess the difficulties and results of salvage surgery for patients who have undergone neoadjuvant treatment for NSCLC.

Methods: In this study, we retrospectively analyzed patients who underwent salvage surgery after neoadjuvant treatment for NSCLC. We included patients who underwent salvage surgery due to local or regional recurrence of NSCLC from January 2010 to December 2016. The study included 72 patients who met the inclusion criteria. The analysis was performed using descriptive statistics.

Results: Of the 72 patients, 51.4% were male, and the median age was 64 years. The most common primary tumor location was the lung (89.7%). The majority of patients had stage IV disease at presentation (72.2%). The median follow-up time was 31 months. The overall survival rate at one, two, and five years was 61.1%, 41.9%, and 26.7%, respectively. The most common causes of death were lung cancer recurrence (47.9%) and metastatic disease (25.6%). The most common surgical procedures performed were pulmonary resection (64.4%), bronchial dissection (46.4%), and mediastinal lymphadenectomy (40.9%). Complications included postoperative fever, pneumonia, and hemorrhage.

Conclusions: Salvage surgery for NSCLC recurrence is a challenging procedure with significant morbidity and mortality. However, it can provide long-term survival for selected patients.

Keywords: lung cancer, salvage surgery, neoadjuvant treatment, NSCLC

P1.08-071 SURGERY FOR LUNG CANCER WITH MEDIASTINAL LYMPH NODE METASTASIS: EFFECTIVENESS OF EXTENDED BILATERAL MEDIASTINAL LYMPHADENECTOMY
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Background: The role of surgery in the treatment of non-small-cell lung cancer (NSCLC) with clinically manifested mediastinal node metastasis is controversial even in resectable cases. Hata et al. used scintigraphy in the selection of patients for resection. They considered bilateral mediastinal lymphadenectomy contributes the survival of the patient with NSCLC. Due to anatomical limitations, it is difficult to perform complete dissection of superior mediastinal lymph nodes through the thoracotomy. We devised extended bilateral mediastinal lymphadenectomy and lung resection through a median sternotomy (ND3) for Left NSCLC, and reported that it can allow for complete dissection of all stations of mediastinal lymph nodes. The aim of this study is to add knowledge on mediastinal lymphadenectomy by evaluating the feasibility and efficacy of our ND3 operation. Methods: We retrospectively studied 283 patients who underwent ND3 operation due to Left NSCLC, from January 1988 till December 2015. All operations were performed through the median sternotomy. The lymph nodes around the right and left recurrent laryngeal nerves were dissected. In 2000-2013, the 5-year survival rates of patients who received it did not include induction chemotherapy-radiotherapy were 63.0% and 34.8%, respectively. Conclusion: The survival rate after surgical therapy for Pancoast tumor significantly improved over the three decades. Preoperative chemotherapy-radiotherapy and the selection of an approach based on the tumor location contributed to the improvement.

Keywords: surgical approach, lung cancer, Pancoast tumor, induction chemotherapy-radiotherapy

P1.08-072 THE RESULT OF COMPLETION PNEUMONECTOMY FOR THE LOCAL RECURRENT LUNG CANCER AFTER RADICAL LOBECTOMY
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Background: Retrospective review on the result of completion pneumonectomy (CP) for the local recurrent non-small cell lung cancer (NSCLC) following the radical lobectomy, performed by a single institution. Methods: From 1995 to 2015, 12 consecutive patients underwent CP for cure of loco-regional recurrent NSCLC. Eleven out of these were the cases with recurrent tumor at resection margin of previous surgery and the rest was the case with multiple metastatic diseases with local remaining lung. The right CP was performed for 5 patients (31.6%) and the left CP for 7 (58.3%). Results: Operative mortality was 0% and major complications occurred in 3 patients (25%). The operations were performed by the posterior lateral thoracotomy for 7 patients, and CP by anterior approaches (median sternotomy or hemi-clamshell thoracotomy). The control of hilar components was achieved through an intra-pericardial route in all cases. In two cases, the infiltration of the recurrent tumors were confirmed in the carinal bifurcation. Thus, the completion “sleeve” pneumonectomy was performed. The complete resections were achieved in all patients. Mean observation period was 1313 days after CP at the time of this investigation. Four patients deceased including 2 cancer re-relapse death and 2 cancer unrelated death. There are 8 survivors for more than one year after CP including 4 patients surviving without cancer relapse (mean survival time (MST) of 1241 days) and 4 surviving with either local or distant cancer relapse (MST > 1354 days). Among those 4 survivors with cancer relapse, 3 patients were treated with molecular targeted drugs after gene-mutation survey for susceptibility of specific molecular targeted drugs using tumor specimen harvested from CP surgery. Another patient with cancer relapse was found to be unsuitable for any type of molecular targeted drugs, thus treated with cisplatin based conventional anti-cancer protocol. Five year survival rates for the entire series was 66.7%. Conclusion: Completion pneumonectomy has been considered as a complex and high risk surgical procedure, however, due to the recent progresses made in the surgical techniques and post-operative management, the CP in the setting of locally recurrent NSCLC became safe and favorable treatment option. More importantly, tumor specimen obtained by the CP can be used for selecting the updated molecular target drugs which might be helpful for patient’s long term survival.

Keywords: Surgery, completion pneumonectomy, recurrence, lung cancer
P1.08-073 EXPERIENCE OF THIRD PRIMARY LUNG TUMORS AFTER TREATMENT OF FIRST AND SECOND PRIMARY LUNG CANCER
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Background: Widespread adoption of lung cancer screening and development of high-resolution computed tomography (HRCT) have led to a marked increase in the detection of early lung cancer in Japan. After curative resection for early lung cancer, second primary lung cancers develop in a significant proportion. The majority of these cancers are detected at an earlier stage because of careful follow-up using HRCT. In our experience, more than 80% of these patients were treated with surgery or radiation therapy, and some of them have acquired with long-term survival. Recently we have experienced with third primary lung tumors in long-term survivors. In this paper, we review the incidence, management, and outcome of third primary lung tumors. Methods: Between April 1996 and March 2016, 1194 patients underwent complete resection for primary lung cancer in our institution. Of these individuals, patients who developed a third primary lung tumor were selected for this study. Results: Of 1194 consecutive patients, 105 patients (8.8%) developed second primary lung cancers, and 11 patients (1%) of them developed third primary lung tumors. The patients included 10 men and one woman. The initial resection for primary lung cancer was lobectomy in 9 patients and segmentectomy in 2. Surgical resection for second primary lung cancer was performed in 8 patients, and radiation therapy was performed in 3. Four of the 11 patients underwent resection for third primary lung tumors. One patient had completion pneumonectomy, 1 had segmentectomy, and 2 had wedge resections. Five patients were treated by radiation therapy. The two remaining patients received best supportive care. Survival after resection of first primary lung cancer ranged from 50 months to 185 months, with a median survival of 138 months and an average survival of 137 months. Currently, 4 patients are alive without evidence of recurrence. Among them, three patients were treated by their third pulmonary resection, and one patient was treated by radiation therapy. Conclusion: During 20 years, third primary lung tumors were diagnosed in only 11 patients (1%). But long-term survivors after resection of lung cancer are increasing. Careful follow-up and early detection of second primary lung cancers using HRCT will increase the experience of treatment for third primary lung tumors. In our little experience, aggressive surgery for third primary lung tumors may improve survival.

Keywords: third primary lung tumor, radiation therapy, lung cancer, Surgery

P1.08-074 EFFECT OF INTRAPLEURAL PERFUSION HYPERTHERMIC CHEMOTHERAPY IN NON-SMALL CELL LUNG CANCER WITH PLEURAL SEEDING
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Background: Pleural seeding is generally associated with poor prognosis in advanced non-small cell lung cancer (NSCLC). Although palliative chemotherapy is the mainstay modality for these patients, intrapleural perfusion hyperthermic chemotherapy (IPHC) may be a good alternative. The aim of this study was to evaluate the efficacy of IPHC and predictive factors for longer survival in NSCLC with pleural seeding. Methods: From 2003 to 2016, 51 patients who underwent IPHC for NSCLC with pleural seeding at the perfusion hyperthermic chemotherapy (IPHC) may be a good alternative. The Background: Pleural seeding is generally associated with poor prognosis in advanced non-small cell lung cancer (NSCLC). Although palliative chemotherapy is the mainstay modality for these patients, intrapleural perfusion hyperthermic chemotherapy (IPHC) may be a good alternative. The aim of this study was to evaluate the efficacy of IPHC and predictive factors for longer survival in NSCLC with pleural seeding. 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Background: The prognosis in patients with distant metastases of NSCLC is poor. Surgical resection of isolated distant metastases in NSCLC patients is not widely accepted and chemotherapy is usually administered. The study was aimed to evaluate the long-term results and prognosis after surgical resection of oligometastases in NSCLC patients. Methods: 139 patients with isolated distant metastases of NSCLC (M1a – 38, M1b – 101) operated on in our clinic from 1998 to 2011 were included in the retrospective trial from the prospective database. Solitary brain metastasis was diagnosed in 82, pleural metastases in 21, contralateral lung in 17, adrenal metastases in 11, others – in 8 patients. Synchronous metastases were detected in 61 (43.9%), metachronous – in 78 (56.1%) patients with pleural dissemination lung resection with pleurectomy followed by PDT was carried out. The primary lung cancer was completely resected in all cases. Surgery included pneumonectomy – in 17, lobectomy/bilobectomy – in 112 and sublobar resection – in 10 patients. Median follow up is 52 months. Results: Postoperative complications were registered in 10 (7.2%) patients, mortality – 2.2%. Median survival after pulmonary resection and removal of brain metastasis was 23.0 months, contralateral lung resection – 12.0, after lung resection with pleurectomy – 11.0 and adrenalectomy – 9.0 months. 5-year survival after lung resection and brain metastasectomy was 20.6%, contralateral lung resection – 12.0%, lung resection and pleurectomy (limited pleural spread) – 10.7%. No one survived more than 2 years after adrenalectomy. Survival of patients in N0-1 cases was significantly better in all groups: after brain metastasectomy - 34.3% vs 0%, contralateral lung resection – 28.0% vs 0%, pleural dissemination – 4.7% vs 0% in N2 positive patients with median survival 19.0 and 8.0, 15.0 and 8.0, 23.0 and 10.0 months respectively. Overall survival was worse in synchronous group if compare with metachronous detection: after brain metastasectomy 10.0% and 19.8%; contralateral lung resection 0% and 32.0%, with median survival 18.0 and 25.0; 11.0 and 21.0 months respectively. In N2 positive cases was confirmed that positive N2 status (p<0.001) and synchronous detection of oligometastic disease (p=0.002) were independent unfavorable prognostic factors. Conclusion: Aggressive surgery in patients with oligometastatic NSCLC is justified in selected patients with solitary brain, contralateral lung metastasis and limited pleural dissemination, especially in N0-1 cases and metachronous disease. Surgical resection should be whenever avoided in patients with oligometastatic lung cancer and positive N2 status.

Keywords: lung cancer, Oligometastatic disease, Surgery

P1.08-079 SULVAGE SURGERY AFTER DEFINITIVE RADIOTHERAPY OR CHEMORADIOThERAPY FOR LUNG CANCER
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Background: Reports of salvage surgery especially bronchoplasty after definitive radiation therapy for locally advanced lung cancer are small. In addition, reports of surgery after stereotactic body radiotherapy (SBRT) are also small. Methods: Between 2011 and 2015, 3 patients who underwent salvage pulmonary resection after definitive radiation therapy (Group A) and 3 patients after SBRT (Group B) were identified. Results: Group A: One of two patients who underwent bronchoplasty failed in anastomosis failure. A 40-year-old woman underwent right upper sleeve lobectomy after chemo- radiation therapy including bevacizumab for primary lung adenocarcinoma (cT3N2M0 Stage IIIA). Two months after surgery, anastomosis dehiscence occurred. She underwent right completion pneumonectomy after preparing an omental flap. Bronchial stump was closed in overholt method with wrapping of omental flap. After surgery, left kidney and supraclavicular lymph node metastasis were detected, she was administered crizotinib. She is alive at 48 months after surgery. The other two patients are alive without recurrence at 8 and 35 months, respectively. Group B: The dose of radiation was 48Gy (12 Gy x 4 fractions ). Period from SBRT until surgery was 14, 18, 30 months, respectively. One patient underwent SBRT for second lung cancer after left upper lobectomy for first lung cancer. He died of respiratory failure on 103 days after surgery. The clinical courses of other two patients were uneventful. One patient died of distant metastasis at 7 months, and other one is alive without recurrence at 8 months. There were no severe adhesion on both hilar and chest wall after SBRT. Conclusion: Caution is needed in the salvage pulmonary resection after chemo-radiation therapy including bevacizumab. On the other hand, there was not strong influence to the bronchial stump after SBRT.

Keywords: definitive radiotherapy, lung cancer, Surgery
Background: Bilobectomy for lung cancer is considered a high risk procedure for the increased postoperative complication rate and the negative impact on survival. We analyzed the safety and the oncologic results of this procedure.

Methods: We retrospectively reviewed patients who underwent bilobectomy for lung cancer between October 1998 and December 2015. Age, gender, bilobectomy type and indication, complications, pathology, stage, and survival were analyzed. Results: Bilobectomy was performed on 166 patients (122 men; mean age, 62 years. There were 87 upper-middle and 79 middle-lower bilobe resections. Indications were tumor extending across the fissure in 37 (22.3%) patients, endobronchial tumor in 64 (26.5%), extrinsic tumor or nodal invasion of bronchus intermedius in 70 (42.2%), and vascular invasion in 15 (10%). An extended resection was performed in 25 patients (15.1%). Induction therapy was performed in 47 patients (28.3%). Thirty-day mortality was 1.2% (n=2). Overall morbidity was 43.4%. Mean chest tube persistence was 7 days (range, 6-46 days). Overall 5-year survival was 58%. Significance differences in survival were observed among different stages (stage I, 70%; stage II, 55%; stage III, 40%; p<0.0003) and the N status (N0, 69%; N1, 56%; N2, 40%; p<0.0005). Extended procedure (p<0.0003) and superior bilobectomy (p<0.0008) adversely influenced survival. Multivariate analysis demonstrated that an extended resection (p=0.01), an advanced N disease (p=0.02), and an upper-mild lobectomy (p=0.02) adversely affected prognosis. Conclusion: Bilobectomy is associated with a low mortality and an increased morbidity. Survival relates to disease stage and N factor. Optimal prognosis is obtained in patients with lower-middle lobectomy without extension of the resection.

Keywords: lung tumor, Bilobectomy, Surgery

Background: Surgical treatment of non-small cell lung cancer (NSCLC) invading the spine is controversial. We evaluated surgical results and long-term outcome of patients with NSCLC who underwent vertebral resection (VR) due to the infiltration by lung tumor. Methods: Retrospective analysis of 16 consecutive patients undergoing VR for NSCLC invading the spine between 1998 and 2015 was performed. Ten patients (62.5%) received induction chemotherapy, 21 patients (10.5%) had a complete response after induction chemotherapy. VR was performed in 10 patients (50%); two of these patients had a massive hemoptysis leading to death; 33 patients had pulmonary complications, 28 cardiac, 17 air leaks. Overall 5- and 10-year survival was 50% and 39%, respectively. Five- and 10-year survival for stages I and II versus stage III was, respectively, 66% versus 32% and 56% versus 20% (p<0.001). Five-year survival was 61% for N0 and N1 nodal involvement versus 28% for N2, respectively; 10-year survivals were 45% versus 28% (p<0.001). IC did not influence survival. Multivariate analysis yielded advanced stage, N2 status, and squamous cell carcinoma as negative prognostic factors. Conclusion: PA reconstruction is safe, with excellent long-term survival. Our results support this technique as an effective option to pneumonectomy for patients with lung cancer.

Keywords: lung tumors, Surgery

Background: The safety and efficacy of hyperthermic pleural lavage (HTPL) with cisplatin in patients who have undergone cytoreductive surgery pleurectomy/decortication (PD) for isolated chemoresistant pleural metastases (PM). This may be an alternative treatment for patients with isolated pleural metastases with controlled primary disease. Methods: After Health Care System and Cancer Committee approval, 10 patients with unilateral chemo resistant pleural metastasis were registered prospectively. The patients’ primary sites of malignancy were under control for a median of 40 months (range, 28-76). Patients underwent a unilateral radical PD and lymph node dissection, 60 minute pleural lavage (1,500 - 1,700 cc/min) with 225 mg/m2 of cisplatin at 42°C. Cisplatin levels were drawn at time zero, 1 hour, 4 hours, and 24 hours after completion of HTPL. Results: Median age was 53 years (range, 38-64), 7 patients (70%) were women. Primary tumor: breast 5, colon 2, and thymic, renal cell and anal cancer 1 each. Surgical approach was anterior thoracotomy in 9 patients (90%). Morbidity included atrial fibrillation in 3 (30%), and acute respiratory distress syndrome in 1 (10%). Median hospital stay 7 days (range, 4-14). Serum cisplatin levels peaked at 4 hours after lavage; none to toxic range. Median dose of cisplatin was 386 mg (range, 299-450); no patient developed renal insufficiency. Median follow up was 10 months (range, 1-11). 8 patients had no signs of malignant disease at last follow up; 1 patient (anal cancer – 6 months) developed local recurrence and 1 patient (renal cell cancer – 9 months) developed contralateral pleural disease. All patients experienced improved quality of life, respiratory function, and reduced pleuritic pain. Conclusion: Surgical cytoreduction of chemoresistant PM followed by HTPL with cisplatin was well tolerated with no cisplatin-related toxicities. Early results are promising. This novel treatment for patients with isolated secondary PM represents the first series reported. Longer follow-up is warranted to determine a survival and quality of life advantage as well as defined inclusion and exclusion criteria.

Keywords: pleural metastasis hyperthermic lavage

Background: Pulmonary artery (PA) reconstruction for lung cancer is technically feasible with low morbidity and mortality. We assessed our experience with partial or circumferential resection of PA during lung resection. Methods: Between 1998 and 2015, we performed PA angioplasty in 150 patients with lung cancer. Seventy-five patients received induction chemotherapy (IC). Partial PA resection was performed in 146 cases. PA reconstruction was performed by running suture in 113 and using a pericardial patch in 33. A circumferential PA resection was performed in 4 patients and reconstruction was made by a custom-made bovine pericardial conduit each. Bronchial sleeve resection was associated in 56 cases. Thirty-two patients had stage I disease, 43 stage II, 51 IIIA, and 17 IIIB. Seven patients had a complete response after IC. Results: Thirty-day mortality was 3.3% (n=5); two of these patients had a massive hemoptysis leading to death; 33 patients had pulmonary complications, 28 cardiac, 17 air leaks. Overall 5- and 10-year survival was 50% and 39%, respectively. Five- and 10-year survival for stages I and II versus stage III was, respectively, 66% versus 32% and 56% versus 20% (p<0.001). Five-year survival was 61% for N0 and N1 nodal involvement versus 28% for N2, respectively; 10-year survivals were 45% versus 28% (p<0.001). IC did not influence survival. Multivariate analysis yielded advanced stage, N2 status, and squamous cell carcinoma as negative prognostic factors. Conclusion: PA reconstruction is safe, with excellent long-term survival. Our results support this technique as an effective option to pneumonectomy for patients with lung cancer.

Keywords: lung tumors, Surgery
P1.08-084 TREATMENT FOR ELDERLY PATIENTS WITH CLINICAL STAGE I NON-SMALL CELL LUNG CANCER; SURGERY OR STEREOTACTIC BODY RADIOTherAPy?

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Background: The number of elderly lung cancer patients requiring surgery has been increasing due to the aging society and less invasive perioperative procedures. Stereotactic body radiotherapy (SBRT) is one of the effective treatments for early stage non-small cell lung cancer (NSCLC). The aim of this retrospective study was to compare the outcome of pulmonary resection to SBRT for elderly clinical stage I NSCLC in our hospital. Methods: Over 80-year-old patients with clinical stage I NSCLC between August 2008 and December 2014 were treated either surgery or SBRT at Nagasaki university hospital. Propensity score matching (PSM) was performed to reduce selection bias in various clinicopathological factors including age, gender, tumor size, carcinoembryonic antigen (CEA), Charlson comorbidity index (CCI), Glasgow prognostic scale (GPS) and forced expiratory volume in one second (FEV1.0) were compared between surgery and SBRT. Results: Pulmonary resection was performed in 57 cases, SABR in 41 cases. In surgery group, operations included 34 lobectomies, 23 limited resection (segmentectomy and wedge resections). Systemic lymph node dissection was 16 and limited dissection was 41 cases. In SABR group, 17 cases (41.5%) were not proven in histology. 27 cases were given 48 Gy by 4 fractions, 14 were 60 Gy by 10 fractions, respectively. No treatment deaths were observed. Before PSM, the 5 year overall survival (OS) in surgery (68.3%) was significantly better than that in SBRT (47.4%, p=0.02). The 5 year disease specific survival (DSS) (94.1%, 78.2%, p=0.17, respectively) was not significant. Similar characteristics were identified in age (82 years), gender, tumor size (2.2 cm), CEA (3.6 ng/ml), CCI (1), GPS (0) and FEV1.0 (1.7 Litter) after PSM. The difference in 5 year OS became insignificant between the matched pairs (57.0%, 49.1%, p=0.56, respectively). 5 year DSS was not significant (87.1%, 70.2%, respectively). Both treatments for elderly clinical stage I NSCLC were acceptable though unknown histology and precise lymph node status still existed as important bias. Conclusion: Surgery for early stage NSCLC is a safe and feasible treatment. SABR could be effective and a good option for early stage NSCLC.

Keywords: surgery, stereotactic body radiotherapy, elderly
P2.01-001 ENRICHMENT-FREE, RAPID METABOLIC ASSAY FOR DETECTION OF TUMOR CELLS IN PLEURAL EFFUSION AND PHERIPHERAL BLOOD
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Background: Current methods for circulating tumor cell (CTC) detection are mostly include an enrichment step and the subsequent immunostaining-based identification of CTCs by epithelial and leukocytes markers. These methods are limited by loss and damage of CTCs during the enrichment and fail to determine the malignancy and drug targets of putative CTCs. Methods: We describe an enrichment-free, metabolic-based assay for rapid detection of tumor cells in the pleural effusion and peripheral blood samples. All nucleated cells are plated on microwell chips that contain 200,000 addressable microwells. These cells are labeled with a fluorescent anti-CD45 antibody (leukocyte marker), a fluorescent glucose analog (2-NBDG) and a dead cell marker (EthD-1). The microwell chips are imaged by a computerized high-speed fluorescent microscope in three colors and the bright filed. A computation algorithm analyzes the images and identify candidate tumor cells that are viable, CD45 negative, and exhibit high glucose uptake (EthD-1/CD45−/2-NBDG−). A micromanipulator is then utilized to retrieve single tumor cells based on recorded addresses for single-cell sequencing. Results: EthD−1/CD45−/2-NBDG− cells are identified as candidate tumor cells. Single-cell sequencing based on a small panel of driver oncogenes (EGFR, KRAS, PIK3CA) shows that >50% of candidate tumor cells are true tumor cells harboring mutations in the panel. Single-cell whole exome sequencing results show all tumor cells have high mutation frequency in driver oncogene and tumor suppressors from Qian’s Human Lung Cancer Panel. Meanwhile, CD45/EthD−1/2-NBDG− tumor cells show heterogeneity in cytokeratin (CK) expression, and only ~40% of these tumor cells are found CK positive.

Conclusion: We have developed a simple and functional-based method to rapidly identify tumor cells with high glucose uptake in the clinical liquid samples without enrichment. These tumor cells are addressable, enabling single-cell manipulation and sequencing. Clinical feasibility of this assay has been established by testing samples from a cohort of patients.

Keywords: circulating tumor cell, lung cancer, enrichment-free, glucose uptake

Table 1. Serum proteins measured in our study.

<table>
<thead>
<tr>
<th>Protein short name</th>
<th>Protein full name</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPG</td>
<td>Osteoprotein</td>
</tr>
<tr>
<td>ePCR</td>
<td>Endothelial cell protein C receptor</td>
</tr>
<tr>
<td>vWF</td>
<td>Von Willebrand factor</td>
</tr>
<tr>
<td>PTX3</td>
<td>Pentraxin 3</td>
</tr>
<tr>
<td>Axl</td>
<td>Tyrosine-protein kinase receptor</td>
</tr>
<tr>
<td>CXCL16</td>
<td>C-X-C motif chemokine ligand 16</td>
</tr>
<tr>
<td>DLL1</td>
<td>Delta-like protein 1</td>
</tr>
<tr>
<td>Cats</td>
<td>Cathepsin 5 (Chloramphenicol acetyl transferase)</td>
</tr>
<tr>
<td>GDF15</td>
<td>Growth differentiation factor-15</td>
</tr>
<tr>
<td>Endostatin</td>
<td></td>
</tr>
<tr>
<td>CD147</td>
<td>Cluster of differentiation 147 (Badigin, EMMPRIN)</td>
</tr>
<tr>
<td>sTNFR1</td>
<td>Tumor necrosis factor receptor 1</td>
</tr>
<tr>
<td>CRP</td>
<td>C-reactive protein</td>
</tr>
<tr>
<td>Alcam (CD166)</td>
<td>Activated leukocyte cell adhesion molecule</td>
</tr>
<tr>
<td>PARC</td>
<td>p53-associated parkin-like cytoplasmic protein</td>
</tr>
<tr>
<td>sCD163</td>
<td>Cluster of differentiation 163</td>
</tr>
<tr>
<td>Gal3BP</td>
<td>Galectin-3-binding protein</td>
</tr>
</tbody>
</table>

Conclusion: Chronic inflammation plays an important role in lung carcinogenesis and in chronic obstructive pulmonary disease (COPD), and is accompanied with alterations in specific serum proteins. Both COPD and lung cancer are associated with smoking behavior, and 40-70% of lung cancer patients have COPD. The aim of the study is to compare levels of specific serum markers related to inflammation, extracellular matrix remodeling (ECM) and endothelial cell activation in patients with lung cancer and COPD.

Methods: Blood samples were collected from 208 lung cancer patients with stage I-IIIA disease before surgery in addition to blood samples from 47 COPD patients, stage I-II (4 patients in stage I, 16 in II, 19 in III and 8 in IV). Six of COPD-patients used oral steroids, 28 used inhaled corticosteroids. Serum levels of various markers were measured by enzyme immunoassays. Results: Of 127 proteins (table 1), 9 were significantly elevated in the COPD group compared to lung cancer group including proteins associated with lung cancer in other studies as DPG, PTX3, ePCR, GDF15 and endostatin. Only 3 proteins, CRP, vWF and GDF15 reflecting systemic inflammation and endothelial cell activation, were more abundant in serum from lung cancer patients, and one of these (CRP) significantly so.

Conclusion: Chronic inflammation plays an important role in both diseases: lung cancer and COPD. However, it seems that inflammation as determined by these selected markers is more pronounced in patients with COPD as most of the biomarkers levels were significantly higher in these patients than lung cancer group.

Keywords: serum biomarkers, lung cancer, Chronic obstructive pulmonary disease (COPD), serum protein
Background: Colorectal cancer (CRC) is one of the most common malignancies and the most frequent cause of cancer-related death in Western countries. In patients with CRC, the presence of liver or lung metastases (LMs) seriously affects survival, and the early diagnosis and resection of LMs significantly improves the outcomes. Unfortunately, the sensitivity of imaging studies in detecting LMs is low, because the onset of solitary pulmonary nodules is common during follow-up, the most part of them are not malignant. The aim of this study was to evaluate the accuracy of serum carcinoembryonic antigen (CEA), vascular endothelial growth factor (VEGF) and matrix metalloproteinase (MMP-7) and cyokeratin-19 fragment (CYFRA 21-1) as predictive markers of LMs from CRC. Methods: We retrospectively reviewed the medical charts of 21 patients with a history of CRC who developed histologically confirmed solitary or multiple PMs. There were 13 (61.9%) men and 8 (38.1%) women, with an overall median age of 65 years (range 31-82 years). Controls were 24 age-matched patients with CRC in whom the presence of PMs was excluded using 18F-FDG PET. The receiver operating characteristic (ROC) curve was used to obtain the optimal threshold value (cutoff point) for each TM. Results: The optimal cutoff was set at 5 ng/mL, 7.5 ng/mL, 250 ng/mL, and 2.8 ng/mL for CEA, VEGF, MMP-7, and CYFRA 21-1, respectively. The sensitivity, specificity, positive (PPV) and negative (NPV) predictive accuracy, and the Area Under the Curve (AUC) were calculated. The logistic regression analysis excluded CYFRA 21-1 from the model, and thus we calculated the results also considering the combination of CEA+VEGF+MMP-7. The area under the ROC curve (AUC) was 0.712 (95% CI: 0.432-0.802).

Conclusion: The periodic assay of CEA+VEGF+MMP-7 together may help to suspect the presence of LMs, suggesting the need to anticipate further evaluations.

Keywords: MMP-7, Lung metastasis, CYFRA-21-1, VEGF

P2.01-004 THE METABOLISM PROFILING OF MULTIPLE TUMOR SUPPRESSOR GENES IN PLASMA CELL-FREE DNA OF PATIENTS WITH NSCLC VS BENIGN TUMORS

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Background: Effective discrimination between lung cancer and benign tumours is a common clinical problem in the differential diagnosis of solitary pulmonary nodules. While most solitary pulmonary nodules are benign, around 20% of cases represent an early stage lung cancer. The presence of cell-free DNA (cfDNA) in plasma of lung cancer patients demonstrates promising diagnostic implications and could be considered as an auxiliary tool in the differential diagnosis of solitary pulmonary nodules by evaluating cancer-specific biomarkers, such as hypermethylated tumor DNA fragments. We developed a simultaneous methylation profiling of 21 distinct tumor suppressor genes (TSGs) in plasma cfDNA using MS-MLPA assay. Methods: The methylation profiling of 21 TSGs in plasma cfDNA of 32 resectable NSCLC (II-Ila) patients and 8 subjects with benign lung nodules (hamartoma, fibrosis, granuloma) was performed using optimized MS-MLPA assay. Results: 25/32 (78%) NSCLC and 8/8 (100%) benign-nodule cfDNA samples presented at least one TSG methylation, however the number of hypermethylated TSGs was much higher in NSCLC group. APC (frequency 18% samples), MLH1 (18%), ATM (13.6%), DAPK1 (13.6%), HIC 1 (13.6%), and RARß (9%) were the most frequently methylated genes in NSCLC, while TIMP3 (75%), MLH1 (25%) and TP73 (37.5%) – in benign patients. Conclusion: The optimized MS-MLPA assay allowed simultaneous detection of multiple methylated TSGs in plasma cfDNA. The MS-MLPA showed good performance in samples with diverse cfDNA concentrations suggesting that methylation detection rate depends on the methylated DNA content in a sample. The study is on-going. The groups are to be extended and other benign lung pathologies evaluated.

Keywords: cell-free DNA, non-small cell lung cancer, gene methylation, biomarker

POSTER SESSION 2 – P2.01: BIOLOGY/PATHOLOGY ANALYSIS OF BODY FLUIDS IN CANCER – TUESDAY, DECEMBER 6, 2016

P2.01-005 EVALUATION OF CIRCULATING TUMORAL MICROMOELI (CTM) AS A PROGNOSTIC FACTOR IN NON-SMALL CELL LUNG CANCER (NSCLC)

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Background: Much has been studied regarding the prognostic role of circulating tumor cells (CTCs) in NSCLC. CTCM (defined as clusters of 3 or more cancer cells detected in peripheral blood) relationship to prognosis was previously published for small cell lung cancer (SCLC), demonstrating worst prognosis for the presence of CTM. No relevant data, however, was published for CTM in NSCLC. The objective of this study is to define the presence of CTM as a prognostic factor for survival in NSCLC and its molecular characteristics. Methods: We performed a retrospective evaluation of 31 metastatic NSCLC patients positive for CTC, which were previously enrolled for CTC research in a single institution. CTC and CTM were detected by ISET (Isolation by Size of Epithelial/Trophoblastic Tumor Cells, Rarecells, France®). Included patients had metastatic disease treated in multiple lines of cytotoxic treatment. Analysis included frequencies, demographic characteristics and survival variables, including Progression Free Survival (PFS) and Overall Survival (OS), with PFS as primary endpoint. The PFS and OS were calculated based on the date of first CTC collection and first progression after collection (PFS) or death (OS). Molecular characterization was performed by immunocytochemistry for Transforming Growth Factor beta receptor (TGFßR) and Matrix Metalloproteinase 2 (MMP2). Results: The primary endpoint was not met. Presence of CTM did not have statistically significant influence on PFS or OS in our population. Eight patients were positive (CTM+) and 23 were negative (CTM-) for CTM. Median follow-up was 13.3 months (m). Median age was 65.5 years in CTM- and 66.9 years in CTM+ patients. Remaining demographic variables were balanced between groups. All patients had progressive disease and 9 were still alive at the time of analysis. Median PFS (mPFS) was 6.9m for CTM- and 4.5m for CTM+, with p=0.59. Median OS (mOS) was paradoxically greater in CTM+, without statistical significance (27.3m for CTM- and 31.6m for CTM+; p=0.83). Molecular characterization did not have any prognostic impact on both CTM- and CTM+ groups. No patient was positive for TGFßR and 2 CTM+ patients were positive for MMP2 (10/31 patients with isolated CTCs positive for MMP2). Conclusion: This retrospective analysis showed no impact on survival for the presence of CTM in NSCLC, which was opposite to findings of positive prognostic value of CTM for SCLC where CTM was a negative factor for survival. Molecular
Characterization also did not show differences between groups. The findings warrant further evaluation in dedicated research.

Keywords: non-small cell lung cancer, circulating tumor cells, survival, circulating tumor microemboli

POSTER SESSION 2 – P2.01: BIOLOGY/PATHOLOGY ANALYSIS OF BODY FLUIDS IN CANCER – TUESDAY, DECEMBER 6, 2016

P2.01-006 SENSITIVE DETECTION OF CTCs IN THORACIC MALIGNANT TUMORS WITH “UNIVERSAL” CTC-CHIP
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Background: Circulating tumor cells (CTCs) are tumor cells shed from primary tumor and circulate in the peripheral blood. CTCs, as a surrogate of distant metastasis, can be potentially useful in diagnosing and monitoring therapeutic effects in malignant tumors. Among a variety of systems for detection of CTCs, the “Cellsearch” is the only approved system for clinical use. However, EpCAM-negative tumors, such as those originating from non-epithelial cells and those undergoing epithelial-mesenchymal transition (EMT), cannot be captured with the “CellSearch” that is an EpCAM-based isolation system. Therefore, we have developed a novel polymeric microfluidic device (“Universal” CTC-chip) that can capture CTCs with or without EpCAM expression (AACR 2015). In the present study, we examined CTCs-detection performance of the CTC-chip in patients with thoracic malignant tumors (lung cancer [LC] as an “EpCAM-positive” tumor and malignant pleural mesothelioma [MPM] as an “EpCAM-negative” tumor) in comparison with that of the CellSearch. Methods: Peripheral blood sampled from each patient was divided and subjected to quantitative evaluation of CTCs with the CTC-chip as well as with the “CellSearch”. The CTC-chip, coated with an anti-EpCAM antibody, was used to capture CTCs in the blood samples (n=10) from lung cancer patients. To capture CTCs in the samples (n=11) from MPM patients, the CTC-chip was coated with an antibody against podoplanin that is expressed on the mesothelioma. After immuno-staining for cytotakin and CD45 on the chip, a captured cell containing Hoechst-positive nucleu and cytoterin-positive/CD45-negative cytoplasm was judged as a CTC. The CTC-count for each sample was represented as the number per 7.5mL of the blood. Results: The median CTC-count detected with the CTC-chip in LC was 50 (range, 0-270), which was significantly higher than that of the median CTC-count (0; range, 0-47) with the “CellSearch”. In the peripheral blood sampled from MPM patients, CTC was detected in only one patient using the CellSearch, but was detected in all 11 patients with the median CTC-count of 144 (range 0-470). Conclusion: The “universal” CTC-chip achieved higher performance in detection of CTCs of thoracic malignant tumors as compared with the CellSearch.

Keywords: circulating tumor cell (CTC), lung cancer, mesothelioma

P2.01-008 SIRE NEXT GENERATION SEQUENCING PANEL: EFFECTIVE DIAGNOSTIC TOOL FOR CIRCULATING FREE DNA ANALYSIS
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Background: Tissue availability is a crucial point in NSCLC. The introduction of Liquid Biopsy allows to determine circulant biomarkers, specifically using free DNA. To simultaneously analyze multiple patients sample at high sensitivity, Next Generation Sequencing (NGS) can be narrowed to target a limited number of actionable genes. Here we prospectively applied a lab-developed narrowed gene panel (SiRe) to produce a DNA library covering actionable mutations in six genes (EGFR, KRAS, NRAS, BRAF, cKIT and PDGFRα). Methods: This daily clinical practice study was performed on cfDNA obtained from Non Small Cell Lung Cancer blood samples (plasma and serum) prospectively collected either prior to treatment administration in patients without tissue availability (n = 46) or after a progressive disease (n = 19) from a first line gefitinib (n = 14) or crizotinib (n = 5) therapy. Results: SiRe detected an activating EGFR mutation in 4/46 (8.9%) cases and in 17/30M in 9/19 (47.4%) at the time of tumor progression. Using tissue data as gold standard, the SiRe panel showed a sensibility of 90.5% and specificity of 100%. Conclusion: The SiRe panel is an effective tool enabling the implementation of NGS for cfDNA mutational profiling in molecular pathology practice.

Keywords: NGS, liquid biopsy, NSCLC, TKIs

POSTER SESSION 2 – P2.01: BIOLOGY/PATHOLOGY ANALYSIS OF BODY FLUIDS IN CANCER – TUESDAY, DECEMBER 6, 2016

P2.01-009 SERIAL QUANTITATIVE ASSESSMENT OF PLASMA CIRCULATING TUMOR DNA BY DIGITAL NGS IN PATIENTS WITH LUNG CANCER
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Background: Detection of circulating tumor DNA (ctDNA) by digital NGS in patients with lung cancer is an established tool for the determination of tumor burden and can be used to monitor disease progression and response to therapy. However, the serial assessment of circulating tumor DNA (ctDNA) has not been systematically evaluated. Here we report a serial assessment of circulating tumor DNA (ctDNA) by digital NGS in a cohort of patients with non-small cell lung cancer (NSCLC).

Methods: A total of 30 patients with NSCLC were enrolled in the study. Plasma was collected at diagnosis, before systemic therapy, during systemic therapy and after treatment failure. The circulating tumor DNA (ctDNA) was isolated from plasma using the QIAamp Circulating Nucleic Acid Kit (Qiagen). The ctDNA was sequenced using Ion Torrent personal Genome Machine (PGM) on Ion Sphere Particles (Konelab) using a Thermus aquaticus-strand displacement polymerase-based protocol. DNA was isolated from tissue biopsy and serum of all the subjects and methylation-specific PCR of APC, DAPK, and GSTP1 was carried out after bisulfite conversion. Association of DNA methylation with various clinicopathological parameters and survival was determined in lung cancer patients. Results: The methylation rates of APC, DAPK, and GSTP1 in tissue biopsy were 83.1%, 83.1%, and 78.1% for lung cancer patients and 72.9%, 70%, and 70% for cancer-free controls. The methylation rates of APC, DAPK, and GSTP1 in serum were 52.5%, 30.6%, and 65.6% for lung cancer patients and 14.3%, 18.6%, and 30% for cancer-free controls. In lung cancer patients, all three genes were methylated at significantly higher frequency in tissue biopsy than matched serum samples. No significant correlation was observed between methylation of any of these genes with clinicopathological parameters, including survival. Conclusion: Present study did not demonstrating any evidence suggesting the role of promoter DNA methylation of APC, DAPK, and GSTP1 in lung carcinogenesis. However, follow-up of cancer-free controls, who were positive for DNA methylation, is required to confirm their role in early stages of lung carcinogenesis.

Keywords: DNA methylation, MS-PCR, Tumor suppressor genes, lung carcinoma

POSTER SESSION 2 – P2.01: BIOLOGY/PATHOLOGY ANALYSIS OF BODY FLUIDS IN CANCER – TUESDAY, DECEMBER 6, 2016

P2.01-009 SERIAL QUANTITATIVE ASSESSMENT OF PLASMA CIRCULATING TUMOR DNA BY DIGITAL NGS IN PATIENTS WITH LUNG CANCER
Yue Zhang1, Jay Gong2, Hong Li3, Weijie Ma4, Kimberly Banks5, Huiyu Wen1, Elizabeth H Moore6, Richard Lamman4, Tianhong Li1
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Background: Next generation sequencing (NGS) has been increasingly used in oncology practice but proven practically difficult when serial tumor specimens are needed. The objectives of this study were to determine feasibility and explore clinical utility of serial NGS analyses of circulating tumor DNA (ctDNA) in patients (pts) with advanced solid tumors undergoing treatment. Methods: ctDNA digital NGS was performed by a CLIA-certified lab (P4gene panel with mutant allele fraction (MAF) quantification). ctDNA results were retrospectively analyzed and decreases/increases/stability of molecular tumor load (MTL) defined here as MAFs of 3 truncal driver mutations were correlated with clinical and radiographic response to treatment (response, progression, or stable disease, respectively). Results: From Jan 2015 to July 2016, 38 consecutive pts with advanced lung tumors (8 LUAD, 5% LUSC, 5% SCLC, 5% NOS) receiving treatment (Table) had serial ctDNA analyses (median 2, range 2-7). ctDNA alterations were detected at least once in 37 (97.4%) pts. Changes in MTL correlated with or predicted all (95% CI, 82.0-99.8%) radiological and/or clinical responses except for the patient with no genomic alteration detected. MTL results clarified response status when radiographic responses were difficult to assess in 9 (28%) of pts with either complex pleural disease (n=6), pneumonitis during PD-1 inhibitor therapy (2). Two MTL change patterns were observed: 1) clonal changes while receiving targeted therapy, including EGFR (12), ALK (3), MET (2), ERBB2 (2); global changes to PD-1 inhibitors, chemotherapy or radiation. Representative tumor response maps will be presented. Table. Summary of tumor types and cancer treatment.

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Targeted Therapy</th>
<th>Immuno-therapy</th>
<th>Chemo-therapy</th>
<th>Radiation</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>LUAD</td>
<td>14</td>
<td>8</td>
<td>7</td>
<td>3</td>
<td>32</td>
</tr>
<tr>
<td>LUSC</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>SCLC</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>NOS</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>All</td>
<td>16</td>
<td>9</td>
<td>10</td>
<td>3</td>
<td>38</td>
</tr>
</tbody>
</table>

Conclusion: Serial liquid biopsies and ctDNA digital NGS are feasible and clinically useful in monitoring MTL, and genomic alterations during cancer treatment, especially in situations when radiographic responses are equivocal. Prospective evaluation of impact on clinical decision making is warranted.

Keywords: plasma, Circulating Tumor DNA, lung cancer, digital next generation sequencing.
Background: Lung cancer is the leading cause of cancer death worldwide. 25-30% of lung cancers are histologically squamous cell carcinomas (SCC). Despite recent advances in immunotherapy for lung SCC, traditional cytotoxic chemotherapies currently remain the mainstay of treatment. However, over the course of treatment, patients with lung SCC inevitably acquire chemotherapy resistance. This results in poor overall survival of advanced stage lung SCC of only 9 to 11 months. Repetitive exposure of lung cancer cell lines to chemotherapeutic drugs enables investigation of molecular mechanisms of acquired chemotherapy resistance in vitro. We are studying the role of miRNAs in this process. MiRNAs are small non-coding nucleic acids that regulate gene expression. They are involved in numerous cellular pathways, including therapy resistance. MiRNA serve as biomarkers and have recently become therapeutic targets or therapeutics themselves. Methods: We induced chemotherapy resistance in lung SCC cell lines LUDLU-1, Calu-1, SK-MES-1 in vitro by repetitive drug treatment over a period of 6 – 12 months. Agents used to develop resistance included Cisplatin, Gemcitabine, Paclitaxel and Vinorelbine. Cell viability after 3 days of chemotherapy treatment was measured by MTT assay and drug dose causing a 50% growth inhibition (IC50) was calculated. Total RNA including miRNA was extracted. Expression of 754 miRNA was measured by TaqMan OpenArray Human MicroRNA array. Results: After 15–25 cycles of chemotherapy lung SCC resistant cells showed a statistically significant increase in IC50 values: Cisplatin up to 12.4 (n-fold); Gemcitabine 40.2 – absolute resistance (n-fold); Paclitaxel 30.9 – 110.1 (n-fold); Vinorelbine 4.6 – 19.3 (n-fold). Resistance was stable and passed on to daughter cells. MiRNA expression of resistant cells was compared to parental, drug sensitive cells and is illustrated by heatmaps and volcano plots. Analysis of expression patterns revealed upregulation and downregulation of specific miRNAs in drug resistant cells. We are currently investigating the function of these dysregulated miRNAs in promoting chemotherapy resistance. Further, we are testing if certain miRNA are suitable targets to improve chemotherapy response. Conclusion: We identified changes of miRNA expression patterns after induction of chemotherapy resistance with various drugs used for lung SCC treatment. These findings may lead to development of new predictive biomarkers and to new miRNA-based drugs.

Keywords: chemotherapy, Squamous cell carcinoma, miRNA, Resistance

POSTER SESSION 2 – P2.01: BIOLOGY/PATHOLOGY
ANALYSIS OF RNA – TUESDAY, DECEMBER 6, 2016

P2.01-013 HA-LIPOSOME NANOCARRIER CONTAINING CD44 siRNA AS A TARGETED CHEMOTHERAPY TO CD44 RELATED CHEMORESISTANT NON-SMALL CELL LUNG CANCER
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Background: Chemotherapy to non-small cell lung cancer (NSCLC) remains a big limitation; chemo-resistance which has been reported regulating by one of cancer stem cells (CSC) marker cluster determinant (CD) 44 expression in NSCLC. Here, we demonstrated that the importance of CD44 in chemo-resistance of NSCLC, subsequently, develop and evaluate the hyaluronan (HA)-liposome as a drug delivery system for overcoming chemo-resistance by efficiently delivery CD44 targeting siRNA to NSCLC cells. Methods: First, the relationship between expression of CD44 and sensitivity of the chemotherapy was evaluated in NSCLC cells (H1299, H1703, H1793, H1435, H2087, H358, H522, H460) using flow cytometry (FACS) and MTT assay. The expression of CD44 was confirmed as inversely proportion to the sensitivity of the chemotherapy in these NSCLC cells. Furthermore, in order to confirm that correlation between CD44 expression and chemo-resistance of NSCLC, we generated and characterized cisplatin resistant cell lines, and indicated that CD44 expression on resistant cells significantly increased compared to wild type cells. Results:

Figure 1. CD44 siRNA effectively improved the resistance of cisplatin by HA-liposome carrier for resistant NSCLC therapy.

Chemo-sensitivity of resistant cells are directly associated with expression of CD44 by knockdown of CD44 expression using siRNA. For overcoming drug-resistance in lung cancer, we developed a HA-liposome drug delivery system which can specifically target to CD44, effectively delivered CD44 siRNA to CD44 overexpressed resistant NSCLC cells. And, the HA-liposome (CD44 siRNA) successfully inhibited the expression of CD44 on resistant cells and improved the sensitivity to cisplatin. Conclusion: We demonstrated the correlation of chemo-resistance and expression of CD44 in NSCLC, and successfully developed HA-liposome drug delivery system for significantly inhibit the expression of CD44. This study supported future investigation HA-liposome (CD44 siRNA) as possible chemotherapy carrier for targeting CD44, to assess for inhibiting chemo-resistance using various drug delivery in NSCLC.

Keywords: lung cancer, chemo-resistance, drug delivery

POSTER SESSION 2 – P2.01: BIOLOGY/PATHOLOGY
ANALYSIS OF RNA – TUESDAY, DECEMBER 6, 2016

P2.01-014 MIR-3941: A NOVEL MICRORNA THAT CONTROLS IGBP1 EXPRESSION AND IS ASSOCIATED WITH MALIGNANT PROGRESSION OF LUNG ADENOCARCINOMA
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Background: Immunoglobulin (CD79A) binding protein 1 (IGBP1) binds to PP2Ac and exerts an anti-apoptotic effect. We have already reported that IGBP1 overexpression occurs during the course of malignant progression of lung adenocarcinoma (Sakashita S et al., Pathol Int. 2011). However, the molecular mechanism of IGBP1 overexpression is still unclear. A few reports have documented mutation, hypomethylation, or amplification of IGBP1, but only one study has suggested that down-regulation of miR-34b leads to high expression of IGBP1 (L-P Chen et al. Oncogene. 2011). In this study, we have detected miR-3941 as another functional microRNA that influences the expression status of IGBP1. Methods: We performed microRNA array analysis using total RNA extracted from fresh specimens of invasive lung adenocarcinoma (IGBP1+) and minimally invasive adenocarcinoma (IGBP1-). We compared the results of microRNA array with microRNAs listed in...
TargetScan (a microRNA database) that would potentially bind to IGBP1. Using reverse transcription-quantitative PCR (RT-qPCR), we analyzed the expression levels of candidate microRNAs in frozen specimens of lung adenocarcinoma. We also validated these microRNAs by checking IGBP1 expression and cell proliferation after they had been transfected into lung adenocarcinoma cell lines (A549, PC-9) and confirmed the direct effect of the microRNAs by luciferase reporter assay. Results: Using microRNA array and TargetScan, we selected 6 microRNAs (miR-34b, miR-138, miR-374a, miR-374b, miR-1909, miR-3941). RT-qPCR analysis showed that these microRNAs were down-regulated in invasive adenocarcinoma (IGBP1+) relative to adjacent normal lung tissue (IGBP1-) (Fig1A). We transfected these microRNAs into lung adenocarcinoma cell lines, and all of the microRNAs suppressed IGBP1 expression. Among these microRNAs, miR-34b and miR-3941 depressed luciferase activity by targeting 3'UTR-IGBP1 in the luciferase vector (Fig1B).

Conclusion: We have found that miR-3941 targets IGBP1 in addition to miR-34b. Down-regulation of both microRNAs can lead to high expression of IGBP1, and this is thought to be associated with progression of lung adenocarcinoma.

Keywords: IGBP1, microRNA, Adenocarcinoma, lung

P2.01-015 DIFFERENTIALLY EXPRESSED MICRORNAS IN LUNG ADENOCARCINOMA INVERT EFFECTS OF COPY NUMBER ABBERRATIONS OF PROGNOSTIC GENES
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Background: Across multiple cancer histologies, many significantly down-regulated genes reside within chromosomal regions with increased number of copies, and vice versa. These “paradoxical genes” have been usually ignored as a noise, but could be a consequence of epigenetic regulatory mechanisms, including microRNA-mediated control of mRNA transcription. Methods: To identify paradoxical genes in lung adenocarcinoma (LUAD) we curated and analyzed gene expression and copy number aberrations across 1,064 LUAD samples, including newly-generated aCGH data from 65 samples. We then analyzed 9 LUAD microRNA expression studies to compile a list of consistently deregulated microRNAs. Finally, using microRNA-gene networks from mirDIP, we examined possible association between microRNAs and paradoxical genes. Results: We identified 85 genes whose differential expression consistently contrasts the aberrations of their copy numbers. 70 genes were validated using TCGA-LUAD data. We showed that paradoxical expression of these genes is associated with 19 microRNAs, whose significant deregulation in LUAD has been consistently reported. Importantly, these genes form a clinically significant prognostic signature.

Fig 1

Conclusion: Paradoxical gene expression, caused by microRNA deregulation, is preserved across patient cohorts, and forms a prognostic LUAD signature.

Keywords: microRNA, prognostic signature, Copy number aberrations, lung adenocarcinoma

P2.01-016 ANALYSIS OF 5 DIFFERENTIAL MIRNA EXPRESSION IN NSCLC PATIENTS
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Background: There are two main types of lung cancer: non small cell lung cancer (NSCLC) which represents 80-85% cases of lung cancer and small cell lung cancer (SCLC) which is about 10-15% cases of lung cancer. The 5-year survival rate for patients with lung cancer vary depending on the stage of the cancer when it is diagnosed. Unfortunately, most of patients with lung cancer are diagnosed on later stage of disease (stage III and IV). In our research we try to find marker among miRNA that can predict occurring of lung cancer on the earlier stage. Methods: Isolation of miRNA from plasma was performed by miCURY RNA Isolation Kit - Biofluids (Exiqon) from NSCLC patients and
controls. Synthesis of cDNA and qPCR were carried out using mirCURRY LNA\textsuperscript{TM} Universal RT microRNA PCR with LNA\textsuperscript{TM} enhanced PCR Primers (Exiqon). Statistical calculations were executed on TI samples as a Pre-eliminary data. Results: Results are shown in the following table.

<table>
<thead>
<tr>
<th>miRNA</th>
<th>negative avg</th>
<th>negative SE</th>
<th>positive avg</th>
<th>positive SE</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>hsa-miR-15a</td>
<td>0.6453</td>
<td>1.09545</td>
<td>0.651</td>
<td>&lt;0.01</td>
<td>↓</td>
</tr>
<tr>
<td>hsa-miR-15b</td>
<td>3.37265</td>
<td>3.9688</td>
<td>0.651</td>
<td>&lt;0.01</td>
<td>↓</td>
</tr>
<tr>
<td>hsa-miR-432</td>
<td>8.3116</td>
<td>7.8844</td>
<td>0.651</td>
<td>&lt;0.01</td>
<td>↓</td>
</tr>
<tr>
<td>hsa-miR-144-3p</td>
<td>5.66905</td>
<td>10.20915</td>
<td>0.651</td>
<td>&lt;0.01</td>
<td>↓</td>
</tr>
<tr>
<td>hsa-miR-660-5p</td>
<td>2.16481</td>
<td>3.20695</td>
<td>0.651</td>
<td>&lt;0.01</td>
<td>↑</td>
</tr>
<tr>
<td>hsa-miR-320</td>
<td>2.0232</td>
<td>1.67568</td>
<td>0.037</td>
<td>&lt;0.01</td>
<td>↓</td>
</tr>
<tr>
<td>hsa-miR-485-3p</td>
<td>-0.03218</td>
<td>-0.23965</td>
<td>0.5048</td>
<td>&lt;0.01</td>
<td>↓</td>
</tr>
</tbody>
</table>

Conclusion: We assessed level of 5 different miRNAs circulating in the blood of NSCLC patients using qPCR. Our initial results show that different miRNA can be used to stratify patients and miRNA. Expression of hsa-miR-451a is decreasing in NSCLC versus negative control. Interestingly up-regulated hsa-miR-660-5p was recently described as a prognostic marker in breast cancer but our result preliminary results showed constant decrease in hsa-miR-660-5p expression in all patients’ groups vs controls. The examination on the bigger cohort of patients is necessary to receive a more statistically significant and conclusive data.

Keywords: cell-free microRNA, biomarkers, miRNA expression profiling, NSCLC.

**POSTER SESSION 2 – P2.01: BIOLOGY/PATHOLOGY**
**ANALYSIS OF RNA – TUESDAY, DECEMBER 6, 2016**

**P2.01-017 CIRCULATING MiRNAs IN LUNG CANCER ARE ASSOCIATED TO PRO-TUMORIGENIC AND IMMUNOSUPPRESSIVE MICROENVIRONMENT**

**Orazio Fortunato, 1 Cristina Borza, 1 Giovanni Centone, 2 Massimo Milione, 2 Davide Conte, 1 Mattia Boeri, 1 Carla Verli, 1 Linda Calzolari, 1 Francesca Andriani, 1 Luca Roz, 1 Veronica Huber, 2 Agata Cova, 1 Chiara Camisaschi, 1 Chiara Castelli, 1 Lucia Rivoltini, 1 Claudio Tripodo, 2 Ugo Pastorino, 1 Gabriella Sozzi, 1 Tumor Genomics Unit, Department of Experimental Oncology and Molecular Medicine, Fondazione IRCCS Istituto Nazionale Dei Tumori Int, Milan/Italy, 2Anatomic Pathology Unit, Department of Pathology and Laboratory Medicine, Fondazione IRCCS Istituto Nazionale Dei Tumori Int, Milan/Italy.

**Background:** We previously reported the identification of diagnostic miRNA signatures in plasma samples of lung cancer patients detected by low dose computed tomography (LDCT) screening. Circulating miRNAs are released into the bloodstream by different mechanisms such as passive leakage from damaged cells or active secretion through extracellular-vesicles or protein complexes Methods: To evaluate the potential origin and the release of the 24 miRNAs of the diagnostic signature we analyzed their expression by real-time or digital PCR in both cells and conditioned medium (CM) from cancer cell-blocks were analyzed by miRNAs in situ hybridization (ISH). Modulation of miRNAs after in vitro treatments known to induce changes associated to changes observed in circulating miRNAs signatures. Results: 24-miRNAs analysis showed higher abundance in specific cellular components such as mir-145 in fibroblasts, mir-126 in endothelial cells, mir-133a in skeletal muscle cells or mir-451 and 142-3p in hematopoietic cells. Generally, tumor cells showed lower levels of miRNA compared to bronchial epithelial cells. MiRNAs specific localization in lung tissue was confirmed by ISH. We observed that mir-451 is specifically expressed in lung interstitial alveolar walls while mir-126 by endothelial cells outside the tumor bulk; mir-145 is characteristic of fibroblast and muscle cells and mir-142-3p of hematopoietic cells, fibroblast and muscle whereas mir-21 is over-expressed in the tumor. The analysis of miRNAs in CM showed that miRNAs secretion is correlated with cellular expression for most cell types (Pearson correlation range: 0.41-0.80). Interestingly, platelets and granulocytes were the components that mostly secreted miRNAs. In vitro experiments showed that endothelial cells under hypoxic condition up-regulated mir-145 and that mir-21 was up-regulated and secreted in lung cancer-associated compared to normal fibroblasts. Interestingly, during conversion of T lymphocytes into T regulatory cells up-regulation of mir-19b and mir-320 was observed whereas mir-15b and mir-197 were up-regulated in the conversion of macrophages into M2 phenotype. Modulation of miRNAs in immune and stromal cells was consistent with up-regulation of the same miRNAs observed in plasma samples. Conclusion: Our findings on the origin of circulating miRNAs support the conclusion that plasma miRNAs are heterogeneous and secreted by different cellular components of lung microenvironment rather than by tumor cells. In particular, we demonstrated that a pro-tumorigenic and immunosuppressive microenvironment contributes to the de-regulation of miRNAs observed in plasma of lung cancer patients.

Keywords: lung cancer, microRNA, microenvironment

**P2.01-018 DIFFERENTIAL MiCRONa EXPRESSION PROFILE BETWEEN YOUNG AND OLD LUNG ADENOCARCINOMA PATIENTS**

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**Background:** Lung cancer is the leading cause of cancer related mortality and approximately 80% is represented by non-small cell lung cancer (NSCLC). In the last decade, age of patients at diagnosis has decreased, with an incidence of approximately 13.4% in patients under 50 years. Previous studies have hypothesized that lung cancer in young patients could represent a separated clinicalpathological entity, however it is still controversial whether younger patients have a different outcome compared with their older counterparts. MicroRNAs (miRNAs) have recently been defined to play a key role in cancer pathogenesis and their aberrant expression has been suggested as a potential biomarker of prognosis in lung adenocarcinoma. To understand the molecular features of young and old adenocarcinoma patients, we investigated the expression levels of a panel of miRNAs selected from recent literature.

**Methods:** Thirty-five lung ADC from patients under 50 years old were enrolled as the younger group and thirty-five ADC older than 50 years were collected as the older group. After miRNA isolation from formalin-fixed and paraffin-embedded tumor tissues, the expression levels of 30 miRNAs were analyzed by NanoString technology and compared between the two groups. Survival data were used to assess the prognostic impact of miRNAs. The software mirGator v3.0 was used to predict the putative pathways targeted by miRNAs. Results: The analysis revealed that 7 miRNAs (mir-25-3p, mir-29c-3p, mir-33a-5p, mir-144-3p, mir-153-3p, mir-342-5p and mir-485-3p) were differently expressed in the two groups (Mann-Whitney U test, p<0.05). All these miRNAs showed higher expression levels in young compared to old patients, and their predicted targets included EGFR, MET, VEGF-A, TP53 and PDGFRA. mir-144-3p had an opposite influence on overall survival, since its up-regulation was associated with a better outcome in young patients (p=0.01) and a worse prognosis in the old group (p=0.03). Conclusion: Our study provides new insights about the role of miRNAs in lung adenocarcinoma occurring in young patients. We observed that lung cancer in young and old patients may be influenced by different regulatory mechanisms since we found 7 miRNAs as downregulated in the older group, probably due to different age-related genetic and epigenetic alterations. Moreover, one of the deregulated miRNAs showed a different prognostic impact in the two groups thus confirming that young and old patients deserve a specific clinical approach. Further validations are needed to better define if an age-based genomic signature could be used as prognostic marker in lung cancer.

Keywords: MicroRNAs, lung adenocarcinoma of the young, Prognosis
**POSTER SESSION 2 – P2.01: BIOLOGY/PATHOLOGY**

**ANALYSIS OF RNA**

**TUESDAY, DECEMBER 6, 2016**

### P2.01-020 IDENTIFICATION OF A THREE-LNCRNA SIGNATURE FOR LUNG CANCER DIAGNOSIS AND PROGNOSIS

**Bin Zhang**, **Hua Zhang**, **Liwei Gao**, **Changli Wang**

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**Background:** Lung cancer is one of the leading causes of cancer-related death in the world. Metastasis is the main cause of death. There is still lack of ideal predictive and prognostic biomarkers. Human lncRNA plays important structural and functional roles in many biology processes. Increasing studies have demonstrated that the abnormal expression of IncRNA is correlated to cancer progress in various types of cancer, and IncRNA is considered as a potential valuable biomarker for diagnosis, treatment and prognosis of cancer. Methods: Here, we investigated the IncRNA expression profile in lung adenocarcinoma with lymph node metastasis and without lymph node metastasis (n=5 vs 5) by microarray assay. Three IncRNAs were selected for further verification by qRT-PCR in a training cohort including 118 paired lung cancer and the adjacent normal tissues and a test cohort including 60 paired tissues. In addition, we analyzed the correlation of the IncRNAs with clinicopathological features and survival. Results: We observed 245 significantly differentially expressed IncRNAs between lung adenocarcinoma with lymph node metastasis and without lymph node metastasis. ROC curve revealed that a 3-IncRNA signature distinguished not only lung cancer with lymph node metastasis from lung cancer without lymph node metastasis but also lung cancer from normal tissue. Moreover, the 3-IncRNA signature showed prognostic value by survival analysis. Multivariable Cox regression analysis showed that the signature was an independent prognostic factor for lung cancer patients. Conclusion: Our results identified a new 3-IncRNA signature for the diagnosis and prognosis of lung cancer, suggesting the potential clinical utility of IncRNA biomarkers in lung cancer.

**Keywords:** lncRNA, lung cancer, biomarker, microRNA

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### P2.01-021 MI RNA DEEP SEQUENCING OF EARLY-STAGE LUNG CANCER PATIENTS TO EVALUATE THE DYNAMIC CHANGE OF CIRCULATING BIOMARKERS IN RESPONSE TO SURGERY

**Daniele Petrielli**, **Stefano Cagnini**, **Annamaria Catino**, **Sara Montagna**, **Francesco Zito**, **Barbara Barrettara**, **Beniamina Pacchioni**, **Caterina Millino**, **Simona De Summa**, **Domenico Galetta**, **Stefania Tommasi**, **Rosanna Lacalamita**

1Molecular Genetics, IRCCS, Istituto Tumori Giovanni Paolo Ii, Bari/Italy, 2University Di Padova, Padova/Italy, 3Medical Oncology, IRCCS, Istituto Tumori Giovanni Paolo Ii, Bari/Italy, 4Pathology Unit, Asl Ba, Bari/Italy, 5Division of Thoracic Surgery, “san Paolo” Hospital, Bari/Italy

**Background:** Early-stage lung cancer patients have a five-year survival rate greater than 70%, however this benefit is not exploited due to late diagnosis. Moreover, for the early-stage patients eligible to surgical intervention the long-term survival is also reduced by the high risk of relapse following surgery. The identification of circulating biomarkers is an attractive and less invasive way to improve the management of lung cancer patients. MicroRNAs (miRNAs) post-transcriptionally modify gene expression and are thus involved in cancer through controlling different cellular processes. Dysregulation of their expression contributes to lung cancer progression both in tissue samples and in the blood stream (plasma/serum). The aim of our study is to assess a miRNA profile from serum patients to identify circulating biomarkers useful to predict surgery outcome in the early-stage NSCLC patients. Methods: 16 early-stage NSCLC patients were enrolled. Serum samples before (pre) and after (post) surgery together with surgical tumor tissue were collected from each patient. Extracted RNA was enriched to construct library. Raw sequencing reads were aligned to hg19 human genome and miRNAs were annotated using miRBase v21. After reads normalization, differentially expressed miRNAs were identified through edgeR package. pvalue < 0.01 was considered as statistically significant. Results: miRNA deep sequencing analysis on 16 NSCLC patients: surgical tissue, pre-surgical and post-surgical serum samples lead to detect a total of 2500 miRNAs. MiRNA expression profile data were explained by the Venn diagram (figure)

**Keywords:** Biomarkers, liquid biopsy, miRNA, next-generation sequencing

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### P2.01-022 A PIWI-INTERACTING RNAs CO-EXPRESSION NETWORK AS A PROGNOSTIC FACTOR IN LUNG CANCER


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**Background:** Early-stage lung cancer patients have a five-year survival rate greater than 70%, however this benefit is not exploited due to late diagnosis. Moreover, for the early-stage patients eligible to surgical intervention the long-term survival is also reduced by the high risk of relapse following surgery. The identification of circulating biomarkers is an attractive and less invasive way to improve the management of lung cancer patients. MicroRNAs (miRNAs) post-transcriptionally modify gene expression and are thus involved in cancer through controlling different cellular processes. Dysregulation of their expression contributes to lung cancer progression both in tissue samples and in the blood stream (plasma/serum). The aim of our study is to assess a miRNA profile from serum patients to identify circulating biomarkers useful to predict surgery outcome in the early-stage NSCLC patients. Methods: 16 early-stage NSCLC patients were enrolled. Serum samples before (pre) and after (post) surgery together with surgical tumor tissue were collected from each patient. Extracted RNA was enriched to construct library. Raw sequencing reads were aligned to hg19 human genome and miRNAs were annotated using miRBase v21. After reads normalization, differentially expressed miRNAs were identified through edgeR package. pvalue < 0.01 was considered as statistically significant. Results: miRNA deep sequencing analysis on 16 NSCLC patients: surgical tissue, pre-surgical and post-surgical serum samples lead to detect a total of 2500 miRNAs. MiRNA expression profile data were explained by the Venn diagram (figure)

**Keywords:** Biomarkers, liquid biopsy, miRNA, next-generation sequencing

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**POSTER SESSION 2 – P2.01: BIOLOGY/PATHOLOGY**

**ANALYSIS OF RNA**

**TUESDAY, DECEMBER 6, 2016**

### P2.01-021 MI RNA DEEP SEQUENCING OF EARLY-STAGE LUNG CANCER PATIENTS TO EVALUATE THE DYNAMIC CHANGE OF CIRCULATING BIOMARKERS IN RESPONSE TO SURGERY

**POSTER SESSION 2 – P2.01: BIOLOGY/PATHOLOGY**

**ANALYSIS OF RNA**

**TUESDAY, DECEMBER 6, 2016**

### P2.01-022 A PIWI-INTERACTING RNAs CO-EXPRESSION NETWORK AS A PROGNOSTIC FACTOR IN LUNG CANCER

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Background: PIWI-interacting RNAs (piRNAs) are small (24-32 nucleotides) non-coding RNAs. Their functions, widely conserved across species, are associated with epigenetic control of gene expression and maintenance of genomic stability by the repression of mobile elements. In humans, ~23,000 piRNAs are known, showing tissue-specific expression patterns. While the aberrant expression of individual piRNAs has been identified in some cancer types, the role of piRNA co-expression networks in the development of lung tumors as molecular markers remains unexplored. By analyzing over 7,000 piRNA transcriptomes from human tumors and non-malignant tissues, we have identified lung cancer (LC) specific expression networks associated with clinically-relevant tumor features and patient prognosis. Methods: We developed a custom small RNA sequence analysis pipeline to generate ~7,000 human piRNA transcriptomes. piRNA expression baseline was deduced from 6,378 piRNA transcriptomes (non-malignant/tumors) from 11 organ sites. In lungs, we analyzed 1,082 tumors and 209 non-malignant samples from two cohorts: BC Cancer Agency (BCCA) and BC Cancer Centre, Toronto/ON/Canada. Network analysis was performed using the weighted gene co-expression network analysis (WGCNA). We evaluated tumor aggressiveness by considering correlation to several clinical parameters, including stage, number of mutations, nodal/distant metastasis, and overall/disease-free survival. piRNA survival signatures were identified using Cox Proportional Hazard Model. Results: A subset of piRNAs were found to have robust expression in somatic tissues. Expressed piRNAs display organ-specific patterns and mainly code to mapping transcripts, suggesting a role in regulation of gene expression. In lungs, 204 piRNAs were consistently expressed in both LC cohorts. Tumor piRNA expression profiles are markedly different from their non-malignant counterparts (133 piRNAs were differentially expressed). The patterns differ between the adenocarcinoma and squamous cell carcinoma, and were influenced by smoking status. Network-based analysis identified piRNA expression changes in two modules of piRNAs are associated with aggressiveness tumor features, such as increased number of mutations, tumor size, and nodal metastasis. Finally, combined expression of piRNAs define signatures associated with patient overall and recurrence-free survival. Conclusion: We provide evidence of somatic, tissue-specific human piRNA expression. In lungs, aberrant expression patterns are associated with well-established etiological factors of cancer and seem to contribute to lung cancer subtype-specific patterns. We discover that specific piRNA-based expression patterns characterize aggressive lung tumors and also exhibit prognostic value. The unique expression patterns of piRNAs offer an opportunity to better understand lung cancer-specific biology as well as develop novel prognostic markers for clinical application.

Keywords: piRNA, expression networks, tumor aggressiveness, lung cancer
Background: Non-small cell lung cancer (NSCLC) is the leading cause of cancer-related death worldwide; however, science has not yet been able to substantially improve the prognosis of lung cancer patients. Accumulating evidence suggests that microRNAs (miRNAs) are key players in the regulation of tumor development and metastasis. Expression of six miRNAs previously shown to play roles in tumor development (miR-146b, miR-122b, miR-21, miR-221, miR-34a, and Let-7a) in other tumor types was examined using real-time RT-PCR in 78 specimens of NSCLC. Results: The results revealed that patients with low expression of miR-146b had a significantly shorter median and mean survival time than those with high miR-146b expression (33.00 and 30.44 months versus 42.0 and 36.90 months, respectively; log-rank test P=0.038). Further, low miR-146b expression level was associated with poor prognosis in NSCLC patients. Univariate Cox hazard regression analysis demonstrated that miR-146b expression levels tended to be a significant prognostic indicator of NSCLC (adjusted hazard ratio=0.482, 95% CI: 1.409-29.593, P=0.016). Multivariate Cox proportional hazard regression analysis showed that miR-146b expression levels were an independent prognostic factor for NSCLC patients (hazard ratio=0.259, 95% CI: 0.083-0.809, P=0.020). Furthermore, the effects of miR-146b on NSCLC cell growth and invasion in vitro were investigated. Our findings demonstrate that ectopic expression of miR-146b suppresses proliferation and colony formation ability of lung cancer H1299 cells in vitro. In addition, miR-146b induced G0/G1 phase arrest in H1299 cells and over-expression of miR-146b inhibited lung cancer cell migration and invasion in vitro. Conclusion: Our findings demonstrate that miR-146b functions as a suppressor miRNA and prognosis predictor in NSCLC.

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P2.01-025 MIR-146B FUNCTIONS AS A SUPPRESSOR MiRNA AND PROGNOSIS PREDICTOR IN NON-SMALL CELL LUNG CANCER
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Background: Non-small cell lung cancer (NSCLC) is the leading cause of cancer-related death worldwide; however, science has not yet been able to substantially improve the prognosis of lung cancer patients. Accumulating evidence suggests that microRNAs (miRNAs) are key players in the regulation of tumor development and metastasis. Expression of six miRNAs previously shown to play roles in tumor development (miR-146b, miR-122b, miR-21, miR-221, miR-34a, and Let-7a) in other tumor types was examined using real-time RT-PCR in 78 specimens of NSCLC. Results: The results revealed that patients with low expression of miR-146b had a significantly shorter median and mean survival time than those with high miR-146b expression (33.00 and 30.44 months versus 42.0 and 36.90 months, respectively; log-rank test P=0.038). Further, low miR-146b expression level was associated with poor prognosis in NSCLC patients. Univariate Cox hazard regression analysis demonstrated that miR-146b expression levels tended to be a significant prognostic indicator of NSCLC (adjusted hazard ratio=0.482, 95% CI: 1.409-29.593, P=0.016). Multivariate Cox proportional hazard regression analysis showed that miR-146b expression levels were an independent prognostic factor for NSCLC patients (hazard ratio=0.259, 95% CI: 0.083-0.809, P=0.020). Furthermore, the effects of miR-146b on NSCLC cell growth and invasion in vitro were investigated. Our findings demonstrate that ectopic expression of miR-146b suppresses proliferation and colony formation ability of lung cancer H1299 cells in vitro. In addition, miR-146b induced G0/G1 phase arrest in H1299 cells and over-expression of miR-146b inhibited lung cancer cell migration and invasion in vitro. Conclusion: Our findings demonstrate that miR-146b functions as a suppressor miRNA and prognosis predictor in NSCLC.

Conclusion: Construction of a phylogenetic tree of lung ACA subclones oriented to stem cells demonstrated that the degree of disruption of a subclone correlated with the degree of similarity of the subclone to stem cells, and with prognosis.

Keywords: stem cells, mass spectrometry, Phylogeny, Subclone heterogeneity

P2.01-026 A MASS SPECTROMETRY BASED STEM CELL-ORIENTED PHYLOGENY OF INTRA-TUMORAL NSCLC SUBCLONES
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Background: Sub-clones within a cancer diverge due to ongoing accumulation of mutations. We sought to characterize the intratumor heterogeneity and phylogenetic relationships among different histological patterns present in lung adenocarcinomas based on mass spectrometric analysis of tumor subclones. Methods: MALDI-TOF mass spectrometry was used to generate proteomics data from different histological regions of 35 resected lung adenocarcinomas based on mass spectrometric analysis of tumor subclones. Results: A total of 128b, miR-21, miR-221, miR-34a, and Let-7a) in other tumor types was examined using real-time RT-PCR in 78 specimens of NSCLC. Results: The results revealed that patients with low expression of miR-146b had a significantly shorter median and mean survival time than those with high miR-146b expression (33.00 and 30.44 months versus 42.0 and 36.90 months, respectively; log-rank test P=0.038). Further, low miR-146b expression level was associated with poor prognosis in NSCLC patients. Univariate Cox hazard regression analysis demonstrated that miR-146b expression levels tended to be a significant prognostic indicator of NSCLC (adjusted hazard ratio=0.482, 95% CI: 1.409-29.593, P=0.016). Multivariate Cox proportional hazard regression analysis showed that miR-146b expression levels were an independent prognostic factor for NSCLC patients (hazard ratio=0.259, 95% CI: 0.083-0.809, P=0.020). Furthermore, the effects of miR-146b on NSCLC cell growth and invasion in vitro were investigated. Our findings demonstrate that ectopic expression of miR-146b suppresses proliferation and colony formation ability of lung cancer H1299 cells in vitro. In addition, miR-146b induced G0/G1 phase arrest in H1299 cells and over-expression of miR-146b inhibited lung cancer cell migration and invasion in vitro. Conclusion: Our findings demonstrate that miR-146b functions as a suppressor miRNA and prognosis predictor in NSCLC.

Conclusion: Construction of a phylogenetic tree of lung ACA subclones oriented to stem cells demonstrated that the degree of disruption of a subclone correlated with the degree of similarity of the subclone to stem cells, and with prognosis.

Keywords: stem cells, mass spectrometry, Phylogeny, Subclone heterogeneity

P2.01-027 A COMPARISON OF FIVE DIFFERENT IMMUNOHISTOCHEMISTRY ASSAYS FOR PROGRAMMED DEATH LIGAND-1 EXPRESSION IN NON-SMALL CELL LUNG CANCER SAMPLES
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Background: Randomised trials have shown treatment with programmed death-1 (PD-1)/programmed death ligand-1 (PD-L1) inhibitors can provide a survival benefit to patients with advanced stage non-small cell lung cancer (NSCLC). PD-L1 expression, determined by immunohistochemistry (IHC) using different protocols, antibodies and thresholds for positivity for different inhibitors, has been reported to be potentially predictive of clinical outcome. The objective of this study was to compare the statistical patterns of prominent PD-L1 IHC assays in clinically relevant NSCLC samples. Methods: Consecutive full sections of 20 NSCLC samples, comprising five each of resection, core biopsy, cytology, and pleural fluid samples, underwent IHC with the following anti-PD-L1 antibodies/autostainers: 22C3/Link 48, 28β/Bondmax, SP142/Bondmax, SP263/Benchmark XT, E1L3N/Benchmark XT according to publicly available protocols. PD-L1 expression were scored manually by pathologists.
according to the percentage of tumour cells (%TC) stained on a continuous scale. Results: Using published tumour cell percentage thresholds for 22C3, 28-8, SP142 and SP263 of ≥50%, ≥15%, ≥5%, and ≥25%, the frequency of PD-L1 positivity assessed as 10%, 15%, 70%, and 15% of cases respectively. When a ≥2% threshold was applied, the corresponding frequencies were 70%, 15%, 95%, 65% respectively, and 55% for EIL3N. Using published thresholds, cases were positive according to 1, 2, 3, and 5 antibodies in 15%, 25%, 30%, 0% and 5% of cases respectively. Sorting of cases according to increasing %TC staining revealed a similar order of cases between antibodies, albeit with differences in %TC quanta and occasional exceptions to the order. Spearman rho analysis indicated %TC staining significantly (p<0.05) correlated between most antibody pairs, except 28-8 and 22C3, 28-8 and SP142, and 28-8 and EIL3N. Unsupervised hierarchical clustering revealed two subgroups, comprising of SP263/22C3/28-8/EIL3N. Conclusion: The classification of cases as PD-L1 positive can vary significantly according to the antibody and protocol used. Differences were more likely due to protocol dependent staining intensities and nominated thresholds for positivity, rather than differences in antibody affinity for different epitopes.

Keywords: immunohistochemistry assays, PD-L1 expression

P2.01-028 PROGNOSTIC SIGNIFICANCE OF GLUT1 AND CAIX EXPRESSION: CORRELATION WITH VOLUME-BASED PET PARAMETERS IN NON-SMALL CELL LUNG CANCER

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Background: Glucose transporter type 1 (GLUT1) and carbonic anhydrase IX (CAIX) represent glucose metabolism and tissue hypoxia, respectively. The purpose of this study is to measure the GLUT1 and CAIX expression and volume-based 18F-fluorodeoxyglucose positron emission tomography (FDG PET) parameters in non-small cell lung cancer (NSCLC) patients and examined the correlations between above parameters and their prognostic significance. Methods: We evaluated GLUT1 and CAIX expression by immunohistochemical methods and volume-based FDG PET parameters in 269 NSCLC patients treated with surgical resection (158 adenocarcinoma, 93 squamous cell carcinoma and 18 other type carcinoma). Metabolic tumor volume (MTV) and total lesion glycolysis (TLG) of NSCLC were measured using pretreatment 18F-FDG PET/CT. Receiver operating characteristics (ROC) curves were used to determine the optimal cut-off values of MTV or TLG. Correlations between GLUT1, CAIX, MTV, TLG, and clinicopathological factors were assessed, and prognostic significance was determined. Results: The GLUT1 expression was identified in 99% of squamous cell carcinoma and 50% of adenocarcinoma. In patients with adenocarcinoma, GLUT1 expression showed positive correlation with MTV or TLG (P<0.012 and P=0.037, respectively). In patients with squamous cell carcinoma, correlation analyses between GLUT1, MTV and TLG were not performed because most cases of squamous cell carcinoma showed GLUT1 positivity. There was no correlation between CAIX expression, MTV and TLG in squamous cell carcinoma and adenocarcinoma. In cases with adenocarcinoma, GLUT1-positive patients had lower overall survival (OS) and lower recur-free survival (RFS) rates than GLUT1-negative patients (P=0.001 and P=0.004, respectively). CAIX expression was not significantly associated with either OS or RFS in squamous cell carcinoma and adenocarcinoma. Patients with high MTV or TLG had significantly lower OS rates and lower RFS rates than patients with low MTV or TLG in adenocarcinoma. High GLUT1, TLG and MTV were significantly associated with adverse clinicopathologic variables. When patients with adenocarcinoma were stratified into two groups (High GLUT1 and TLG vs. the other 3 groups), high GLUT1 and TLG was an independent prognostic marker for OS in multivariate analysis (P=0.003). Conclusion: Our results show that high GLUT1 expression levels were significantly associated with MTV or TLG in patients with adenocarcinoma. High GLUT1 and TLG was an independent prognostic marker for OS. High GLUT1 and TLG can be used to identify a subgroup of patients with adenocarcinoma at high risk of recurrence or progression who may benefit from aggressive chemotherapy or radiotherapy.

Keywords: glucose transporter type 1, total lesion glycolysis, lung adenocarcinoma, Metabolic tumor volume

P2.01-030 PROGNOSTIC IMPACT OF STATHMIN1 EXPRESSION IN PATIENTS WITH NON-SMALL LUNG CANCER

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Background: Stathmin 1 is a cytosolic phosphoprotein that plays a crucial role in the control of cellular division and proliferation by regulating microtubule dynamics. In addition, Stathmin1 is associated with tumor growth and progression. Our study aimed to determine differences in overall (OS) and disease free survival (DFS) in patients with non-small lung cancer (NSCLC) stratified by STMN1 tumor expression. Methods: Using immunohistochemistry, Stathmin1 expression was determined in resection specimens from 423 NSCLC patients. The relationship between Stathmin1 protein expression and overall and disease free survivals was assessed using Kaplan Meier survival curves and compared using log-rank statistics. Cox proportional hazards regression determined the hazard for death stratified by Stathmin1, adjusting for clinicopathological characteristics. Results: The STMN1 protein was expressed in 58% of NSCLC cases, 54% of Adenocarcinoma, 63% of Squamous cell carcinoma, and 100% of large cell non Hodgkin carcinoma. STMN1 expression was significantly associated with advanced T and N factors, advanced pathologic stages, positive lymphatic permeation, positive vascular invasion, and poor or mediate differentiation. STMN1 was a negative prognostic factor for OS (hazard ratio [HR]=2.21, 95% confidence interval [CI]: 1.54-3.169, p<0.001) and DFS (HR=2.685, 95% CI: 1.83-4.022, p<0.001). Multivariable Cox analysis confirmed that STMN1 protein expression was an independent predictor of unfavorable OS (HR=1.480, 95% CI, 1.060 to 2.176; p=0.046) and DFS (HR=1.605, 95% CI, 1.105 to 2.329; p=0.013) in all NSCLC patients, and of an unfavorable DFS (HR=2.128, 95% CI, 1.293 to 3.503; p=0.003) in Stage I NSCLC.
patients. Conclusion: STMN1 expression was an independent prognostic factor for NSCLC, even when restricted to early stage patients.

POSTER SESSION 2 – P2.01 BIOLOGY/PATHOLOGY PROTEINS IN LUNG CANCER AND PROTEOMICS – TUESDAY, DECEMBER 6, 2016

P2.01-031 CCL CHEMOKINES MAY PLAY A IMPORTANT ROLE IN CISPLATIN RESISTANCE

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Background: In the absence of a targetable mutation, cisplatin based chemotherapy is the backbone of NSCLC treatment. However, a diverse patient population combined with complex tumour heterogeneity is hampering its’ clinical utility. Although intrinsic and acquired resistance to cisplatin is common, the mechanisms have not yet been fully elucidated. However, some studies have suggested that inflammatory pathways may play a key role in chemoresistance. The aim of this project is to increase our understanding of inflammatory mediated cisplatin resistance in NSCLC.

Methods: A number of isogenic cell line models of NSCLC (adenocarcinoma, squamous cell carcinoma, large cell carcinoma) cisplatin resistance were utilised to assess the role of inflammation in chemoresistance. These included a sensitive parental cell line (PT) and a matched resistant subtype (PT-R). The cells were screened for NFKB and a number of inflammatory mediators including chemokines and TLRs at the mRNA (RT-PCR/qPCR) and protein level (Western blot/ELISA). A specific NFKB inhibitor, DHMEQ, and recombinant chemokines were employed to further characterise inflammatory pathways in PT and CisR cells in terms of cisplatin sensitivity, proliferation (BrdU ELISA), cellular viability (Cytell Cell Imaging System) and DNA damage response (Comet). An in vivo study was also completed using DHMEQ alone and in combination with cisplatin. Results: A number of NFKB targets and responsive pathways are deregulated in CisR cells compared with their matched sensitive PT cell line. Among others, CCL2 and CCL5 are upregulated in PT and CisR cells, respectively. These results may reflect an alternative pathway whereby PT and CisR cells are able to circumvent cisplatin. Further characterisation is ongoing assessing chemokine specific inhibitors. Although, in vivo data suggests a trend of decreased tumour growth in the DHMEQ cohorts compared with vehicle control, there was no significant effect. However, tumour samples appeared more necrotic with DHMEQ treatment. DHMEQ sensitised CisR cells to cisplatin which is reflected by IHC for necrosis and proliferation. Conclusion: Targeting chemokines downstream of NFKB may provide a means to overcome inflammation mediated acquired and intrinsic NSCLC chemoresistance. Given the increased significance of immunoncology agents to harness the body’s own immune system in the fight against cancer, these agents may also prove fruitful in re-sensitising patients to chemotherapy.

Keywords: non-small cell lung cancer, inflammation, Chemokines, Cisplatin resistance

POSTER SESSION 2 – P2.01 BIOLOGY/PATHOLOGY PROTEINS IN LUNG CANCER AND PROTEOMICS – TUESDAY, DECEMBER 6, 2016

P2.01-032 IMPACT OF PREOPERATIVE SERUM ANTI-60S RIBOSOMAL PROTEIN L29 LEVELS ON PROGNOSIS IN PATIENTS WHO UNDERWENT SURGERY FOR NON- SMALL CELL LUNG CANCER

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Background: Ribosome is a subcellular organelle, which serves as the site of biological protein synthesis. Ribosomal protein L29 (RPL29) is one of the proteins composing ribosome, and it expresses in cell surface as well as in cytoplasm, especially showing its high expression in cancer cells. Methods: We retrospectively reviewed 92 patients who underwent surgical resection for non-small cell lung cancer between June 2010 and January 2017. Preoperative serum anti-RPL29 levels were measured by the indirect enzyme-linked immunosorbent assay. The cut-off value was established by the median of anti-RPL29 levels. Results: The patients consisted of 60 males and 32 females, and their average age was 68.7 years (range: 44–87 years). Adenocarcinoma was the most common subtype (n = 69), which was followed by squamous cell carcinoma (n = 13), adenosquamous cell carcinoma (n = 4), pleomorphic carcinoma (n = 6), and large cell carcinoma (n = 2). Postoperative pathological stage consisted of stage IA (n = 28), IB (n = 28), IIA (n = 11), IIB (n = 2), and IIIA (n = 23). EGFR activating mutations were found in 35 patients (3 adenocarcinomas, 2 adenosquamous cell carcinomas, and 1 pleomorphic carcinoma). The median of anti-RPL29 levels in 92 cases was 0.351. Three-year and five-year overall survival rate was 62.7% and 56.6%, respectively, in the patients whose serum anti-RPL29 level was less than the median, and 90.0% and 83.7%, respectively, in the patients with the median or more of anti-RPL29 levels (P = 0.005). In the multivariate Cox proportional hazard model, anti-RPL29 level being the median or more and pathological stage IA were identified as independent prognostic factors (P = 0.013 and P = 0.017, respectively). Conclusion: Serum anti-RPL29 levels may be a novel prognostic marker for non-small cell lung cancer.

Keywords: non-small cell lung cancer, serum, anti-RPL29, Prognosis

POSTER SESSION 2 – P2.01 BIOLOGY/PATHOLOGY PROTEINS IN LUNG CANCER AND PROTEOMICS – TUESDAY, DECEMBER 6, 2016

P2.01-033 EXOSOMAL PROTEOMICS ANALYSIS REVEAL NEW TARGETS FOR RADIATION-INDUCED LUNG TOXICITY DIAGNOSIS

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Background: radiation-induced lung toxicity (RILT) are observed today in patients who have undergone thoracic irradiation for the treatment of lung malignancy. Radiation-induced damage to normal lung parenchyma remains the dose-limiting factor in chest radiotherapy. However, the radiative dosage is not effective for most of patients because of avoiding RILT. Therefore, novel diagnosis methods reveal individual potential RILT are required. For now, increasing evidence illustrates that exosomes in circulating fluids provide a promising way as biomarkers for noninvasive disease diagnosis. Exosomes are 30–150 nm particles which are released from cells into the extracellular environment and thousands of proteins have been identified in plasma exosomes. Whether exosomal proteomics analysis could benefit lung cancer patients with appropriate radiative dosage and prevent RILT remains to be studied. Methods: Plasma samples were collected from RILT patients with grade I and II, and no RILT individuals matched with age, gender and blood collection time 10 to 30 Gy radiation within 6 months. Plasma exosomes were assessed by 110,000×g ultracentrifugation and visualized by NanoSight equipment. The raw data of exosomal proteomics profiles of RILT patients and no-RILT individuals were generated by LC-MS and its expression were verified by western blot. Results: In the present study, we revealed 17 exosomal protein participated in wounded response and two of them were correlated with RILT clinic stage. AZM (Alpha-2-macroglobulin) was decreased in RILT patients and FGB (Fibrinogen beta chain) was increased in RILT patients. Furthermore, AZM was decreasing from no radiative damage patients to that of RILT grade I to II, and the FGB expression in exosomes showed positive correlation with RILT from low to high level. The patients with low FGB expression in plasma exosomes could tolerate higher radiative dosage until the FGB was upregulated in plasma. Conclusion: LC-MS is an efficient method for exosomal proteomics analysis and we reveal two stable targets AZM and FGB, which could indicate the potential of patients suffering RILT after radiotherapy. The two novel targets could serve as promising diagnosis biomarkers for avoiding RILT.

Keywords: radiation-induced lung toxicity, Exosomal proteomics

P2.01-034 THE PREGNANCY ASSOCIATED ENDOMETRIAL PROTEIN
GLYCODELIN AS A BIOMARKER FOR MALIGNANT PLEURAL MESOTHELIOMA

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Background: Malignant pleural mesothelioma (MPM) is a rare and aggressive tumor with a short survival time arising from the mesothelial cells of the pleura. MPM is mainly associated with asbestos exposure and is a strong inflammatory reaction. The common treatment of MPM combines macroscopic complete resection and adjuvant or neoadjuvant chemotherapy, respectively. Soluble mesothelin and osteopontin are currently available biomarkers for malignant mesothelioma with moderate sensitivity and specificity. Glycodelin is an immune system modulator well described during pregnancy. It is involved in invasion of the trophoblast and in regulation of the immunotolerance between the maternal immune system and the fetus. Methods: With a commercial ELISA, we measured the glycodelin serum concentrations of patients with MPM. In addition, we analyzed the glycodelin gene expression using quantitative PCR and stained glycodelin in formalin-fixed paraffin embedded tissue slides. Results: We found high glycodelin concentrations in the serum of patients with MPM compared to benign lung diseases. Pathological glycodelin serum concentrations exhibited a worse overall survival. Moreover, glycodelin serum levels correlated with tumor response to treatment. A comparison of soluble mesothelin-related proteins (SMRP) and glycodelin in the serum of a large patient cohort demonstrated that the detection of both soluble factors can increase the reliable diagnostic of MPM. Glycodelin mRNA and protein was highly expressed in MPM tumors compared to normal lung tissue. Conclusion: In this study, we first described the expression of glycodelin in MPM. Altogether, glycodelin seems to be a new potential serum biomarker for the aggressive malignant pleural mesothelioma. Keywords: malignant pleural mesothelioma, biomarker, Glycodelin

POSTER SESSION 2 – P 2 0 1 : BIOLOGY/PATHOLOGY PROTEINS IN LUNG CANCER AND PROTEOMICS – TUESDAY, DECEMBER 6, 2016

P2.01-035 PROTEIN AND MOLECULAR ALTERATIONS IN EMT PATHWAYS OF LUNG CANCER: A COMPARATIVE ANALYSIS BETWEEN ADC, SCC, LCC

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Background: The adoption of next-generation sequencing (NGS) may help to identify single nucleotide variants (SNVs), small insertions–deletions (indels), and larger structural variations including chromosomal rearrangements. Many molecular alterations have protein-level associations that can be questioned using immunohistochemistry (IHC). The goal of our study was to investigate the molecular pattern and predictive biomarkers and new genes involved as potential therapeutic targets with an emphasis on the IHC and their translational promise. Methods: We studied 212 formalin fixed and paraffin embedded tissues: 8 high-grade and 20 low-grade neuroendocrine carcinomas (NEC), 102 adenocarcinomas (AD), 65 squamous cell carcinomas (SCC) and 22 large cell carcinomas (LCC), placed in tissue microarrays (TMAs). EGFR, PS3, KRAS, ALK, ERBB2, PTEN, BRAF, VEGF, CD24 and CD44 were examined using IHC and Aperio system. DNA extracted (QIAmp) from a subset was used for sequencing. Results: EGFR, P53, PTEN, BRAF, VEGF were significantly lower in NEC group compared to other subtypes (P<0.05). Overall, LCC have lower protein expression than ADC and SCC, specially P53 and VEGF. We detected several drivers mutation including EGFR 22%(19/80), ERBB2 2%(5/80), immune regulated genes CD276 6.8%(17/80), and CTLA 15.4%(39/80). We observed also EMT gene mutations as CD44 30.7%(78/80), MMP2 2.8%(7/80), VGF 2%(5/80), CDH1 2.4%(6/80), SNAI 20%(16/80), VIM 1.2%(8/80), and TWIST 12%(8/80). Interestingly, a significantly higher CD24 and AXL gene expression was found in ADC and SCC specimens compared to NEC(P=0.001 and P=0.04, respectively). Similar to the protein expression in overall low gene expression was also observed in LCC compared to others. Conclusion: We detected different patterns of protein and gene alteration in LC with predominant low expression in NEC. Furthermore, the high expression of EMT genes as AXL and CD44 observed among ADC and SCC can be a evidence that those genes might be a distinctive RTK in these tumors than in NEC tumor suggesting that targeting these genes will be benefit as anti-cancer treatment. Keywords: Immunohistochemistry, next generation sequencing, epithelial–mesenchymal transition, non small cell lung cancer

POSTER SESSION 2 – P 2 0 1 : BIOLOGY/PATHOLOGY PROTEINS IN LUNG CANCER AND PROTEOMICS – TUESDAY, DECEMBER 6, 2016

P2.01-036 IDENTIFICATION OF A NOVEL ONCOGENIC UBQUITIN-LIKE PROTEIN IN LUNG CANCER EPIGENOME-WIDESPAN ASSOCIATION STUDY (EWAS)

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Background: Lung cancer (LC) is the leading cancer-related cause of death worldwide with a 5-year survival rate of only 8%. Smoking is the main risk factor for lung malignancies, but not every smoker develops LC. DNA methylation alterations in tumor tissue lead to genome instability and thus can contribute to malignant cell transformation. Smoking-associated blood DNA methylation changes have been shown to indicate LC risk. We aimed to investigate differential blood DNA methylation in healthy smokers for the identification of novel oncogenes. Methods: We performed Illumina 450K epigenome-wide DNA methylation arrays for 66 smoking prediagnostic lung cancer case-control pairs. The blood DNA samples for this nested case-control design came from the European Prospective Investigation into Cancer and Nutrition (EPIC) Heidelberg cohort. Differentially methylated candidate CpGs were then tested in lung tumor versus adjacent normal tissue for differential methylation in multiple patient sample sets. Additionally, we tested whether differential methylation leads to differential gene expression in lung tumor tissue. Results: The top candidate CpG found was evaluated in functional LC cell based assays to investigate the consequences of its expression in LC tissue. Results: The top differentially methylated candidate CpGs from EPIC were also found differentially methylated in lung tumor versus adjacent normal tissue. The two top differentially methylated CpGs were located within differentially methylated regions (DMRs) and the proximal or associated genes were differentially expressed in lung tumors. The top DMR revealed the regulation of gene expression by DNA methylation of a downstream ubiquitin E3 ligase. Derepressed expression of that gene was associated with LC cell proliferation, migration and glucose uptake in vitro. The gene was found to be involved in the activation of AKT by mTORC2.

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When the gene was knocked down, apoptotic genes which are suppressed by activated AKT in LC cells were re-expressed. Expression of a cell cycle promoting regulator stimulated by activated AKT was found repressed in LC knock down cells. Conclusion: We identified differential DNA methylation in blood from healthy smokers who later developed LC. The top differentially methylated CpGs were also differentially methylated in lung tumor versus adjacent normal tissue samples. The top DMR lead to expression of a proximal ubiquitin E3 ligase. We showed, that this gene is crucial for the mTORC2-mediated activation of AKT. This ubiquitin E3 ligase has not previously been associated with cancer but our findings identify it as a novel epigenetically deregulated LC oncogene.

Keywords: DNA methylation, Epigenoge-wide association study, lung cancer

Background: Non-diagnostic bronchoscopic or image guided biopsies of small, solitary pulmonary nodules are a common and frustrating clinical conundrum which can cause thoracic oncologists and patients to opt for radical therapy without a pathological diagnosis. As a result, some patients with benign conditions have unnecessarily undergone radical treatment. This study sought to determine if metabolomics profiling of plasma could be used to distinguish early stage NSCLC cases from cancer-free controls. Furthermore, we sought to determine if phenotypic subtypes of NSCLC could be distinguished from one another using metabolomics profiling.

Methods: Frozen preoperative plasma samples from a cohort of 48 early stage NSCLC patients (24 Adenocarcinomas, 24 Squamous Cell Carcinomas) and 24-cancer-free controls obtained prior to surgical resection were randomly selected from a provincial lung cancer biorepository for metabolomics analysis. Plasma samples were uniformly thawed, extracted, and analyzed in triplicate by blinded personnel using ultra high performance liquid chromatography/quadrupole time of flight mass spectrometry (UHPLC-QTOF-MS). After data mining, metabolomics profiles were quantified and normalized using Mass Profiler Professional (Agilent Technologies, CA, USA) and individual metabolites were identified using the Metlin Database. Partial least square discrimination (PLSD) was used as a prediction model to identify metabolomics profiles which effectively clustered NSCLC cases from Controls and Adenocarcinomas from Squamous Cell Carcinomas. Results: More than 17,500 entities were detected using the UHPLC-QTOF-MS technique of which 250 potential metabolomics biomarkers were present in all 72 samples. The PLSD analysis using all detected entities effectively distinguished NSCLC cases from controls with 97% overall accuracy. Several endogenous metabolites were metabolically significantly affected in Adenocarcinoma and Squamous Cell Carcinomas cases compared to controls samples. Some of the identified compounds include biliverdin IX, serotonin, PE15:0/20:2 and 3-ketophosphaginase. In addition, 3-acetamidopropanol, 9,10-dihoxy-hexadecanonic acid and anandamide (20:5-n-3) were found in high concentrations in Adenocarcinoma cases compared to Squamous Cell Carcinomas. Conclusion: Distinguishing patients in the metabolomics profiles was apparent and demonstrated the preliminary feasibility of distinguishing early stage NSCLC cases from controls and adenocarcinomas from squamous cell carcinomas using metabolomics techniques. Validation of this methodology on a larger, prospectively accrued, cohort is planned in order to optimize model fit and to assess the diagnostic and NSCLC subtype discriminatory performance in the clinical setting.

Keywords: NSCLC subtype differentiation, non-small cell lung cancer, metabolomics, lung cancer diagnosis

Background: Chronic obstructive pulmonary disease (COPD) is a progressive, inflammatory lung disease associated with an up to 10-fold increased risk of lung cancer (LC). COPD and LC share common etiologies including genetic susceptibilities and risk factors, such as smoking. This study systematically characterizes the molecular overlap between COPD and LC. Methods: Small airway gene expression data was obtained from subjects with spirometry measurements and DNA methylation data from up to 10-fold increased risk of COPD via spiroometry. The correlation analysis between methylation and mRNA data was performed using a weighted correlation network analysis (WGCNA). Results: A total of 31 genes significantly co-expressed across small airways was negatively associated with FEV1 and preserved in LUAD tumors. Genes in this module were enriched in functions associated with cell cycle progression, and known and/or predicted to physically interact in the protein complex critical to mediating the DNA repair and cell cycle checkpoints (CCND1, CCND2, and CCNB1). Conclusion: The top DMR lead to expression of a proximal ubiquitin E3 ligase, known to regulate expression of genes involved in cell cycle progression. FOXM1 is an essential mitotic protein, known to regulate expression of genes involved in cell cycle progression, as well as stress response to ROS and DNA damage, angiogenesis and metastasis. The correlation analysis between methylation and mRNA data was performed using a weighted correlation network analysis (WGCNA) showed that highly correlated genes across airway expression profiles. Combined module expression (gene expression scores) were used to (1) identify genes co-expressed across small airways, (2) evaluate genes associated with FEV1, and (3) identify genes associated with FEV1. The top DMR lead to expression of a proximal ubiquitin E3 ligase, known to regulate expression of genes involved in cell cycle progression, as well as stress response to ROS and DNA damage, angiogenesis and metastasis.

Background: Smoking is associated with cancer but our findings identify it as a novel epigenetically deregulated LC oncogene.
where CLDN2 IHC score was 0 vs. 2-5 (p=0.009), however, when analyzed separately, none of the histological subgroups showed correlation between CLDN2 expression and overall survival. Conclusion: Our results demonstrated significant claudin expression differences not only between the SCC-AD and SCC-L-AD but also between the L-ADC and ADH histological subgroups, which strongly underlines that L-ADC represents a distinct entity within the ADC group. CLDN1 overexpression is a good prognostic factor in NSCLC, but only in the SCC subgroup.

Keywords: Immunohistochemistry, lung cancer

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**Abstracts**

**Giaccone Stradins University, Riga/Latvia, S422**

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**Romi Biswas**

TUESDAY, DECEMBER 6, 2016

**PROTEINS IN LUNG CANCER AND PROTEOMICS – POSTER SESSION 2 – P2.01: BIOLOGY/PATHOLOGY PROTEINS IN LUNG CANCER AND PROTEOMICS – TUESDAY, DECEMBER 6, 2016**

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**P2.01-040 CXC CHEMOKINE RECEPTOR 3 AND ELR MOTIF NEGATIVE CXC CHEMOKINE LIGAND AXIS IN NON-SMALL-CELL LUNG CANCER**

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Background: CXC group chemokine receptors and ligands are well known for their role in immune response, regulation of angiogenesis, tumour development and stromal composition. Understanding of lung cancer pathogenesis requires comprehensive analysis of cell interaction in tumour microenvironment formed by malignant cells, stromal cells and immune cell infiltrate. CXC chemokine receptor 3 (CXCR3) and ELR motif negative CXC chemokine ligands 4, 9, 10 and 11 (CXCL4, CXCL9, CXCL10 and CXCL11) form an axis which is part of complex tumorigenesis process. Methods: The study recruited 38 patients with NSCLC ranging from stage IA to II A undergoing anatomical pulmonary resection between January 2011 and January 2012. Patients were followed to assess relapse rate and survival. CXCR3 expression and tumour infiltrating immune cells (neutrophils, T helper cells, CD4, cytotoxic T lymphocytes - CD8, B cells - CD20, macrophages - CD68 and plasma cells - CD38) were evaluated in resected tumour specimens by immunohistochemistry. For CXCR3 basic annotation parameters included an evaluation of staining intensity (negative, weak, moderate or strong) and fraction of stained cells (rare, <25%, 25-75% or >75%). Blood samples from peripheral vein and from pulmonary vein draining tumour vascular bed were collected at the time of surgery. Levels of CXCL4, CXCL9, CXCL10 and CXCL11 were measured using ELISA and CXCL gradient was calculated. Pearson test was used to assess statistical relationship between CXCL levels, CXCR3 expression and immune cell infiltrate. Results: Majority of tumour specimens despite heterogeneity showed strong CXCR3 expression which was equally intense in tumour cells and stroma. Correlation between tumoral and stromal expression was very strong (r = 0.86, p < 0.001). Tumoral expression of CXCR3 correlated with total number of tumour infiltrating immune cells (r = -0.58, p < 0.01), number of helper cells (r = -0.5, p = 0.01) and T cytotoxic cells (r = -0.45, p = 0.01). Stromal CXCR3 expression had similar correlation with aforementioned parameters but also included correlation with number of B cells in infiltrate (r = 0.05). Stromal CXCL4 and CXCL10 gradients were measured using ELISA and CXCL gradient was calculated. Pearson correlation coefficient r was 0.86, p < 0.001. Stromal CXCL4 and CXCL10 gradients had significant correlation with number of T helper cells (r = -0.5, p = 0.01) and T cytotoxic cells (r = -0.4, p = 0.01). Moderate statistically significant correlation was found between CXCL4 and CXCL10 gradients and relapse (r = 0.39, r = 0.35, p = 0.05). Conclusion: CXCR3 and ELR motif negative CXC chemokine axis plays role in lung cancer pathogenesis and needs further evaluation for better understanding of tumour immunology.

Keywords: CXC chemokines, CXCR3, Tumour immunology

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**P2.01-041 INTEGRATED PROTEO-GENOMICS ANALYSES REVEAL EXTENSIVE TUMOR HETEROGENEITY AND NOVEL SOMATIC VARIANTS IN LUNG ADENOCARCINOMA**

Romil Biswas, 1 Shaojian Gao, 1 Contance Cutilaro, 2 Xu Zhang, 3 Tanap Maitiy, 1 Corey Carter, 1 Anish Thomas, 1 Arun Rajan, 1 Ken-Ichi Hanada, 1 Young Song, 1 Ziad Abdullaev, 1 Paul Metzler, 1 James Yang, 1 Svetlana Pack, 1 Giuseppe Giacone, 1 Javed Khan, 1 Udyan Guha

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Background: Tumor heterogeneity is a major impediment to targeted treatment response in a variety of cancers, including lung cancer, the commonest cause of cancer death. However, the extent of heterogeneity at the genomic and proteomic level along with its effects on treatment response may be patient-specific. Methods: We undertook comprehensive whole genome, exome or targeted sequencing, together with mass spectrometry-based proteomics analyses on surgically procured lung and lymph node metastatic sites and normal blood from an African American never-smoker lung adenocarcinoma patient who had survived with metastatic disease for over seven years while being treated with single or combination ERBB2-directed therapies. Results: Surprisingly, only 1% of somatic variants were common between the two sites, as revealed by WGS. Interestingly, one novel somatic translocation, PLAG1-ACTA2 was identified in both sites resulting in overexpression of ACTA2 that may have been the driver of early metastasis in this patient. The likely predominant driver of proliferation, ERBB2, was focally amplified along with CDK12, greater in the lung compared to the lymph nodes. However, an ERBB2 L869R mutation was specific to the lymph node. We also discovered a novel CDK12 G879V mutation that was specific to the lung. Isogenic MCF10A cells expressing ERBB2 L869R were more proliferative than those expressing wild type ERBB2. Cells expressing ERBB2 L869R that developed lag in growth sensitivity showed a mesenchymal phenotype, increased migration, and produced significantly more lung metastases than lapatinib-sensitive ERBB2 wild-type cells in a tail vein injection assay, implicating this mutation in repeated progression of lung node metastases. The CDK12 mutation is expected to have resulted in a non-functional kinase, lower expression of DNA damage response genes, greater instability of the lung tumor genome, and increased sensitivity to chemotherapy. Accordingly, there was no metastatic sites evident at autopsy in the lung, suggesting the lung metastatic sites were essentially cured. We further sought to correlate the genomic heterogeneity with alterations in the proteome and phosphoproteome using a resolution mass spectrometry. For this purpose, we first assembled patient-specific database including all somatic variants, as revealed by WGS, from the lung and lymph node to interrogate the mass spectrometry data. Several aspects of the genomic heterogeneity were evident at the protein level. These included the identification of the mutant CDK12 G879V peptide and higher expression of ERBB2 in the lung. Conclusion: The integrated proteo-genomics analyses reveal unprecedented tumor heterogeneity in a patient with lung adenocarcinoma. However, similarities in key tumor driver pathways remain.

Keywords: Proteo-genomics, Tumor heterogeneity, lung adenocarcinoma

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**P2.01-042 T CELLS SUBSETS WITH INF-GAMMA, TNF-ALPHA AND ADA IN DISTINGUISHING TUBERCULOUS FROM MALIGNANT PLEURAL EFFUSIONS**

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Chest, Sohag University, Sohag/Egypt

Background: The differential diagnosis of tuberculous and malignant pleural effusion (PE) is extremely difficult and continues to pose clinical challenges. We aimed to evaluate the utility of pleural fluid Interferon gamma (IFN-γ), Adenosine deaminase (ADA), Tumor necrosis factor-alpha (TNF-α) levels with T cells subsets in diagnostic differential of malignant (MPE) and tuberculous pleural effusions (TPE). Methods: Forty patients with pleural effusion (20 tuberculous and 20 malignant) were included in the study. The percentages of CD3 lymphocyte, CD4 lymphocyte and Treg (CD4 CD25) T cells subsets in differential diagnosis of malignant (MPE) and tuberculous pleural effusions (TPE). Results: The ADA activity, INF-γ and TNF-α concentrations were significantly higher in tuberculous PE (84.22±74.17 vs. 2.31±17.93 IU/ml, P<0.0001, 12.45±76.67 vs. 35.03±21.38 pg/ml : P<0.0001 and 2.61±0.62 vs. 0.3±0.20 IU/ml : P<0.0001 respectively). CD3 cells subsets (CD3 T cells, CD4 T-cells and Treg cells) were significantly higher in TPE than in MPE (76.46% ± 65.29%, P=0.004, 51.21% ± 43.50%, P=0.044 and 16.60% ± 12.43%, P=0.032 respectively). CD3 plus CD4 as well as CD3 plus CD4 plus Treg combinations were all 100% specific for discriminating TPE from MPE. TNF-α plus INF-γ, TNF-α plus ADA, as well as TNF-α plus INF-γ plus ADA, were 100% specific for discriminating TPE from MPE. Furthermore, the specificity of combined diagnostic value of TNF-α, INF-γ, ADA with T cells subsets was 95%. Conclusion: The combinations of pleural fluid INF-γ, ADA, TNF-α levels and T cells subsets could effectively address the challenge of
distinguishing tuberculous pleural effusion from malignant pleural effusion.

Keywords: Pleural effusion, lung cancer, T cells

POSTER SESSION 2 – P.2.01: BIOLOGY/PATHOLOGY


P.2.01-043 PATHOLOGIST AGREEMENT RATES OF PD-L1 TUMOR AND IMMUNE CELL QUANTITATION USING DIGITAL READ, FIELD-OF-VIEW, AND WHOLE TUMOR IMAGE ANALYSIS

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Background: PD-L1 agents have shown clinical efficacy. Recent reports have demonstrated the predictive value of PD-L1 immunohistochemistry (IHC) assessment from immune (IC) and tumor cells (TC) in non-small cell lung carcinoma (NSCLC). While assessing percent staining of TC is a task familiar to pathologists, assessment of IC is novel and possibly challenging. As noted in other studies, digital pathology (DP) with image analysis (IA) has the potential to reduce inter-reader (IR) variation in specific situations. However, the impact of DP-IA on IR variation in the setting of PD-L1 IHC scoring is unknown. We compare the effects of different IA approaches (field-of-view [FOV] vs whole tumor [WT]) in NSCLC samples. Methods: A cohort of 60 NSCLC formalin-fixed paraffin-embedded tissue samples was stained with PD-L1 IHC (SP142). Three pathologists underwent training for IHC-based manual essay and DP IA interpretation. Three scorers independently and blindly scored each case using digital read (DR, no IA but digital assessment on computer monitor), FOV IA, and WT IA. Data was analyzed using pairwise overall percent agreement rates (PA) derived from assay threshold categorical bins. Results: For IC scoring, WT IA significantly improved IR agreement and reproducibility rates as compared to DR and FOV-based approaches (table 1). TC WT IA also showed similar improvements.

Table 1: NSCLC IR OPA rates. PD-L1 IHC scoring threshold 1% (TC1/IC1), DR = 100.0, FOV = 99.7, WT = 90.0.

<table>
<thead>
<tr>
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<th>TC-DR (%)</th>
<th>TC-FOV (%)</th>
<th>TC-WTA (%)</th>
<th>IC-DR (%)</th>
<th>IC-FOV (%)</th>
<th>IC-WTA (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>R1-R2</td>
<td>83.1 (71.5-90.0)</td>
<td>89.8 (79.5-92.3)</td>
<td>98.3 (91.0-99.7)</td>
<td>89.1 (77.0-93.3)</td>
<td>91.5 (81.6-99.3)</td>
<td>100.0 (93.9-100.0)</td>
</tr>
<tr>
<td>R2-R3</td>
<td>94.5 (85.1-98.1)</td>
<td>87.3 (76.0-93.7)</td>
<td>100.0 (93.5-100.0)</td>
<td>76.7 (62.3-86.8)</td>
<td>84.6 (75.5-94.9)</td>
<td>100.0 (93.5-100.0)</td>
</tr>
<tr>
<td>R1-R3</td>
<td>81.3 (70.0-92.0)</td>
<td>85.7 (74.3-92.6)</td>
<td>98.2 (90.6-99.1)</td>
<td>83.9 (72.2-91.3)</td>
<td>95.5 (84.9-98.7)</td>
<td>100.0 (93.6-100.0)</td>
</tr>
</tbody>
</table>

Poster: P2.01: Biology/Pathology

Immune Mechanisms in Thoracic Cancer and Targeted Therapy – Tuesday, December 6, 2016

P.2.01-044 BASELINE PERIPHERAL BLOOD CELL SUBSETS ASSOCIATED WITH SURVIVAL OUTCOMES IN ADVANCED NSCLC TREATED WITH NIVOLUMAB IN SECOND-LINE SETTING

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Background: Nivolumab is the first checkpoint inhibitor approved for the treatment of Squamous (Sq) and Non-Squamous (non-Sq) metastatic NSCLC in second-line setting, showing a survival benefit in randomized phase III trials. The aim of this study is to investigate the potential role of baseline peripheral blood cells in relation to clinical outcomes following nivolumab treatment. Methods: From November 2015 to June 2016, we evaluated 45 patients with Sq (n = 10) and non-Sq (n = 35) NSCLC, previously treated with first-line platinum-based chemotherapy, that received nivolumab 3 mg/kg IV on day 1 of each 2 week treatment cycle. Clinical characteristics (TCs: T-Stage, lymph node involvement, M-Stage) were assessed. Total numbers of leukocytes, myeloid-derived suppressor cells (MDSCs), including both monocytic (Mo-MDSC) and granulocytic (Gr-MDSC) type, regulatory T cells (T-regs), and serum lactate dehydrogenase (LDH) were assessed. Endpoints were correlated with objective response (OR), progression-free survival (PFS, categorized as ≤3 or >3 months) and overall survival (OS). Tumor response was assessed using RECIST criteria, version 1.1, at week 9 and every 6 weeks thereafter until disease progression. Statistical methods were based on univariate analyses (Wilcoxon rank test). Results: The median PFS of the overall study population was 3 months. Data about Gr-MDSCs (identified by flow cytometry as Lin−CD14−CD11b+HLA−DR−), Mo-MDSCs (Lin−CD14+CD11b+HLA+DR−), and absolute eosinophil counts (AEC) were available in 37/45 patients (82%) of treated patients. Baseline absolute numbers of Gr-MDSCs, Mo-MDSCs and AEC were greater in patients with good prognosis (PFS >3 months) and better outcomes. In particular among patients with shorter PFS, the median numbers of Gr-MDSCs, Mo-MDSCs and AEC were significantly lower than those detected in patients with longer PFS (4 vs 13 cell/μl, p<0.01; 4 vs 21 cell/μl, p=0.06; SS vs 15 cell/μl; p=0.02, respectively). No correlation was observed between T-regs, LDH, absolute mononuclear, lymphocyte, granulocyte counts and clinical outcomes. Conclusion: A baseline blood signature characterized by low levels of Gr-MDSCs, Mo-MDSCs and AEC is associated with poor outcome (median PFS ≤3 months) in 67.6% of patients treated with nivolumab. In contrast, patients (32.4%) with high levels of these three biomarkers showed a median PFS significant longer than 3 months. Overall survival analysis is ongoing.

Keywords: NSCLC, Nivolumab, biomarker, Immunotherapy

Poster: P2.01: Biology/Pathology

Immune Mechanisms in Thoracic Cancer and Targeted Therapy – Tuesday, December 6, 2016

P.2.01-045 NINTEDANIB IMPROVES ANTI-TUMOR EFFICACY IN COMBINATION WITH ANTI PD-1 IN SYNGENIC TUMOR MODELS SENSITIVE AND REFRACTORY TO IO INHIBITION

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1 Pathology, Boehringer Ingelheim Rvc, Wien/Austria

Background: Nintedanib, an oral triple-angiokinase inhibitor, has received regulatory approval in combination with docetaxel based on the demonstrated efficacy as a 2nd line treatment for NSCLC patients. Two recently approved immune checkpoint PD1 antagonists have shaken up the established lines of NSCLC therapy. In order to explore the combination potential of Nintedanib with PD1 antagonists, we performed in vivo combination experiments in two syngeneic murine tumor models. Methods: The murine tumor cell lines CT-26 and 4T1 were injected subcutaneously into female BALB/c mice. Established tumors around of 50-100mm³ were randomized into the different treatment groups and treated with vehicle, RPM1-14 (murine anti PD-1, 10mg/kg, i.p., q3or4d), Nintedanib (50mg/kg, p.o., 7d) and RPM1-14 plus Nintedanib. Anti tumor efficacy was determined after 3 weeks of treatment. In a separate pharmacodynamic approach larger tumors of~300mm³ were treated for 10 days followed by FACS analyses of the dissociated tumors for various myeloid cell subsets including monocytes/macrophages and granulocytes (Markers: CD14, CD11b, Ly6C, Ly6G, PD-L1, F4/80), T cells/activation (Markers: CD3, CD4, CD8, CD25, FoxP3, IFN-gamma, PD-1) and NK cells (Markers: CD335/Nkp46). Results:Single agent treatment of CT-26 subcutaneous tumors with RPM1-14 and Nintedanib resulted in anti-tumor effect with T/C values of 45% and 63%, respectively. The combination treatment group after 24 days showed a T/C value of 34%. In the RPM1-14 refractory tumor model 4T1 neither anti-PD1 treatment nor nintedanib showed benefit (T/C=88% and 82%). The combination treatment after 26 days resulted in a T/C value of 38%. The particular immune cell infiltrate and activation state in the different treatment groups will be reported. Conclusion: The combination of angiogenic and immune checkpoint inhibition is an attractive opportunity to improve overall response rates and efficacy based on the dual roles of angiogenic factors in blood vessel formation and immune regulation. In the CT-26 model improved additive and synergistic effects could be demonstrated by combining Nintedanib with anti PD-1. More interestingly, the addition of Nintedanib in the anti PD-1 refractory model 4T1 showed a synergistic combinatorial anti-tumor effect. These data fit well with the hypothesis that interfering with tumor angiogenesis in combination with immune checkpoint inhibition will result in additive and synergistic effects by
Abstracts

positively regulating immune cell function and infiltration.

Keywords: angiogenesis inhibition, immune checkpoint inhibition, combination angiogenesis inhibition and IOD

POSTER SESSION 2 - P2.01: BIOLOGY/PATHOLOGY
IMMUNE MECHANISMS IN THORACIC CANCER AND TARGETED THERAPY - TUESDAY, DECEMBER 6, 2016

P2.01-046 QUANTITATIVE MEASUREMENT OF B7-H3 PROTEIN EXPRESSION AND ITS ASSOCIATION WITH PD-L1 AND TILS IN NSCLC
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Background: B7-H3 (CD276) is a type I transmembrane protein that belongs to the immunoregulatory family including PD-L1 (B7-H1) and is upregulated in multiple malignancies including Non-Small Cell Lung Cancer (NSCLC). Clinical activity of monoclonal B7-H3 blocking antibodies such as Enoblituzumab are under investigation. In this study we measured the levels of B7-H3 protein in NSCLC and studied its association with major tumor infiltrating lymphocyte (TIL) subsets, levels of PD-L1, B7-H4 and clinico-pathological characteristics in three independent NSCLC cohorts. Methods: We used automated quantitative immunofluorescence (QIF) to assess the levels of B7-H3 (clone D9M2L, CST), PD-L1 (clone SP142, Spring), B7-H4 (Clone D1M8I, CST) CD3, CD8 and CD20 in 634 NSCLC cases from 3 retrospective cohorts represented in tissue microarray format. The targets were selectively measured in the tumor and stromal compartments using co-localization with cytokeratin. Associations between the marker levels, major clinicopathological variables and survival were analyzed. Results: Expression of B7-H3 protein was found in 80.4% (510/634) of the cases and the levels were higher in the tumor than in the stromal compartment. High B7-H3 protein expression level (top 10 percentile) was associated with poor survival in two out of three of the cohorts (p < 0.05). Elevated B7-H3 was consistently associated with smoking history across the 3 cohorts, but not with sex, age, clinical stage and histology. Co-expression of B7-H3 and PD-L1 was found in 77.6% of the cases (123/634) and with B7-H4 in 10% (63/634). B7-H4 and PD-L1 were simultaneously detected only in 1.8% of NSCLC (12/634). The expression of B7-H3 was not associated with the levels of CD3, CD8 and CD20 positive TILs. Conclusion: B7-H3 protein is expressed in the majority of NSCLCs and is associated with smoking history. High B7-H3 protein levels may have a prognostic effect in Lung Carcinoma. Elevated levels of B7-H3 are associated with lymphocyte infiltration. Co-expression of B7-H3 with PD-L1 and B7-H4 is relatively low, suggesting a non-redundant biological role of these targets and possibilities for combination therapies using monoclonal antibodies.

Keywords: B7-H3, PD-L1, TILs

P2.01-047 INTRA- AND INTER-OBSERVER REPRODUCIBILITY STUDY OF PD-L1 BIOMARKER IN NON- SMALL CELL LUNG CANCER (NSCLC): THE DREAM STUDY
Wendy Cooper1, Prudence Russell2, Philippe Huot-Marchand3, Maya Cherian4, Edwina Duhig5, David Godbolt6, Peter Jessup7, Christine Kho8, Conull Leslie9, Annabelle Mahar10, David Moffat11, Vanathi Sivasubramaniam12, Amanda Grattan13, Alena Reznichenko14, Ann-Marie Woodgate15, Sephen Fox16

1Tissue Pathology and Diagnostic Oncology, Royal Prince Alfred Hospital, Camperdown/NSW/Australia, 25th, Vincent’S Pathology, Fitzroy/VIC/Austria, 3Real World Evidence, Mapi Group, Lyon/France, 4Department of Anatomical Pathology, The Canberra Hospital, Canberra/ACT/Australia, 5Sullivan Nicolaides Pathology, Tarana/QD/ Australia, 6The Prince Charles Hospital, Chermside/Australia, 7Department of Anatomical Pathology, Royal Hobart Hospital, Hobart/Tas/Australia, 82 Peter MacCallum Cancer Centre, Melbourne/VIC/Australia, 9Pathwest Laboratory Medicine, Nedlands/WA/Australia, 10Department of Anatomical Pathology, Flinders University, Bedford Park/SA/Australia, 11Sydpath, St Vincent’S Hospital, Darlinghurst/NSA/Australia, 12Merc Sharp & Dohme (Australia), Macquarie Park/NWA/Australia, 13Merck Sharp & Dohme (Australia), Macquarie Park/Australia

Background: PD-L1 expression in NSCLC correlates with increased response to pembrolizumab, supporting its role as a predictive biomarker but the reproducibility of pathologists’ scoring of PD-L1 requires further investigation. The primary objective of the DREAM study was to assess the reproducibility of scoring PD-L1 staining by evaluating intra- and interobserver reproducibility for the assessment of PD-L1 expression in NSCLC. The secondary objective was to assess the impact of training on reproducibility. Methods: The study was a blinded, pathologist reproducibility study of scoring PD-L1 expression in NSCLC cases stained with PD-L1 22C3 pharmDx™ kit using the Dako Automated Link 48 Platform. Two pathologists previously trained and certified by Dako scored 789 specimens to form the gold standard. From these specimens 60 were randomly selected to evaluate a 1% cut-point and 60 for a 50% cut-point. Both sample sets were designed to include 50% positive/negative specimens and 20-30 close to each cut-point. Ten pathologists were randomly assigned to two subgroups. Subgroup 1 analyzed all samples on two consecutive days. Subgroup 2 performed the same assessments, except they received a one hour training session prior to the second assessment. Results: The overall percent agreement (OPA) for the analysis of the intra-observer reproducibility was 89.7% (95% CI: 85.7; 92.6) for the 1% cut-point sample set and 91.3% (95% CI: 87.6; 94.0) for the 50% cut-point. The OPAs for inter-observer reproducibility of all ten pathologists were 84.2% (95% CI: 82.8; 85.5) and 81.9% (95% CI: 80.4; 83.3) for the 1% and 50% cut-point sample sets, respectively. There was substantial agreement at both the 1% cut-point (prevalence-adjusted bias-adjusted kappa 0.68 (95% CI: 0.65; 0.71)) and the 50% cut-point (prevalence-adjusted bias-adjusted kappa 0.64 (95% CI: 0.61; 0.67)).

Training was found to have no or very little impact on the intra- or inter-observer reproducibility in subgroup 2. The OPAs for the inter-observer reproducibility assessments were 82.0% and 82.3% for the first and second assessments of the 1% cut-point sample set, respectively, and 78.3% and 81.7% for the first and second assessments of the 50% cut-point sample set, respectively.

The exploratory analyses showed that the sensitivity and specificity of the pathologists assessments, compared with the gold standard assessment, were 84.3% and 93.1%, respectively, for the 1% cut-point and 56.3% and 94.0%, respectively, for the 50% cut-point.

Conclusion: There is high intra-observer reproducibility and substantial inter-observer agreement in pathologists’ assessment of PD-L1 expression in NSCLC at 1% and 50% cut-points.

Keywords: PD-L1, non-small cell lung cancer, Reproducibility

POSTER SESSION 2 - P2.01: BIOLOGY/PATHOLOGY
IMMUNE MECHANISMS IN LUNG CANCER AND TARGETED THERAPY - TUESDAY, DECEMBER 6, 2016

P2.01-048 PAIRED COMPARISON OF PDL1 ASSESSMENT ON CYTOLOGY AND HISTOLOGY FROM MALIGNANCIES IN THE LUNG
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Background: PD-L1 tests have been approved on histological specimens only. More than 1/3 of NSCLC patients are diagnosed on cytology alone. The hypothesis of this study is that cytological cell block material is as good as histological material for PD-L1 analysis. Methods: 86 paired samples of malignancies from the lung (NSCLC = 72, other primary malignancies and metastases = 14), where cytological cell block and histological material were available from the same lesion within 6 weeks were stained for PD-L1 on serial sections with PD-L1 IHC 28-b pharmDx® (28-b pharmDx) and PD-L1 IHC 22C3 pharmDx® (22C3 pharmDx). The partial or complete membrane staining on malignant cells regardless of intensity was assessed as ≥ 1% and ≥ 50% positive.

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There was high agreement between the cytological and histological scores, applying to both pharmDx kits and all cutoffs (Table), not changing by exclusion of cytological cell blocks containing <100 cells nor by exclusion of non-NSCLC. Pearson’s \( r \) were 0.87-0.89. Paired samples with PD-L1 staining heterogeneity on histological material seemed to have lower agreement than samples with homogenous staining. Conclusion: High correlation between staining on cytological cell block material and histological specimens was observed using PD-L1 IHC 28-8pharmDx and PD-L1 IHC 22C3pharmDx, suggesting that cytological material is as good as histological material for PD-L1 IHC analysis. Intra-tumor heterogeneity may contribute to disagreement and more research on the influence of staining heterogeneity is warranted.

Keywords: Cytology/histology, agreement, PD-L1, NSCLC

**POSTER SESSION 2 – P2.01: BIOLOGY/PATHOLOGY**

**IMMUNE MECHANISMS IN THORACIC CANCER AND TARGETED THERAPY – TUESDAY, DECEMBER 6, 2016**

**P2.01-049 A COMPARATIVE STUDY OF PD-L1 IHC 28-8 PHARMDX AND PD-L1 IHC 22C3 PHARMDX ON MALIGNANCIES FROM THE LUNG**

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Background: PD-L1 tests as predictive biomarkers for anti-PD-1 immunotherapy for NSCLC have been developed independently and use different assays and cutoffs for positivity. A more flexible PD-L1 testing would allow for efficient use of sparse tissue and pathology resources. The aim of this study was to evaluate the agreement between PD-L1 IHC 28-8 pharmDx (28-8 pharmDx) and PD-L1 IHC 22C3 pharmDx (22C3 pharmDx) assays in patients with malignancy in the lung. The comparison was made on cytological cell blocks as well as on histological material. Methods: Paired samples of malignancies from the lung (NSCLC = 73, other primary malignancies and metastases = 14) where cytological cell block material and histological material seemed to have lower agreement than samples with homogenous staining. Conclusion: High correlation between staining on cytological cell block material and histological specimens was observed using PD-L1 IHC 28-8pharmDx and PD-L1 IHC 22C3pharmDx, suggesting that cytological material is as good as histological material for PD-L1 IHC analysis. Intra-tumor heterogeneity may contribute to disagreement and more research on the influence of staining heterogeneity is warranted.

Keywords: Cytology/histology, agreement, PD-L1, NSCLC

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High OA, APA and ANA were found for agreement between 22C3pharmDx and 28-8pharmDx on cytological clot material, as well as on histological tissue for all cutoffs. The APA at cutoff 50% positivity was the lowest (80%); the CIs were however wide due to small number of positive samples at this cutoff. Pearson’s \( r \) were 0.96-0.97. Conclusion: High correlation between PD-L1 IHC 22C3 pharmDx and PD-L1 IHC 28-8 pharmDx was observed on both cytological and histological specimens, suggesting that these assays may be used interchangeably in testing of lung tumors for PD-L1 expression. However, more data is needed to alter current guidelines.

Keywords: PD-L1, NSCLC, Cytology/histology, agreement
Background: Small Cell Lung Cancer (SCLC) is a highly aggressive tumor. Although most of SCLC cases are sensitive to chemotherapy, the prognosis of SCLC is still dismal. Programmed death-ligand 1 (PD-L1), which is expressed on many cancer cells, has been reported as a predictive biomarker for immune checkpoint inhibitors treatment in advanced non-small-cell lung cancer. However, expression of PD-L1 in SCLC has not been fully studied. Methods: Totally 72 surgical specimens of SCLC (42 primary, 30 metastases) were involved in this study. Only 5 cases had received neoadjuvant chemotherapy before surgery while 67 cases did not. Rabbit anti-PD-L1 monospecific antibody (Spring Bio, SP142,1100) was used on tissue microarray to detect the expression of PD-L1 on these cases. Results: PD-L1 was strongly expressed on the membrane of tumor cells of 8 cases (11.1%) and in the immune stroma of 35 cases (46.6%). Another 29 cases (40.3%) were totally negative for PD-L1 staining. Expression of PD-L1 was significantly associated with clinicopathological parameters (age, gender, T staging, nodal status, TNM staging, vascular invasion and treatment). Conclusion: PD-L1 was expressed in more than half of SCLC cases and correlated with tumor sites. These data may provide useful information for future research or clinical trial on immune checkpoint therapy for SCLC.

Keywords: PD-L1, small cell lung cancer, IHC, immune checkpoint inhibitors therapy

P2.01-054 LUNG CANCER PD-L1 MRNA EXPRESSION PROFILE AND CLINICAL OUTCOMES - A CLINICAL ANALYSIS FROM THE CANCER GENOME ATLAS AND CANCER CELL LINE ENCYCLOPEDIA

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Background: Programmed death ligand 1 (PD-L1) has become one of the most studied biomarkers in early, and advanced non-small cell lung cancers (NSCLC). Conflicting results have been reported in the literature on the value of PD-L1 in predicting survival in surgically resected lung cancers. Our aim was to evaluate mRNA PD-L1 expression and survival based on the data available from the Cancer Genome Atlas (TCGA), and Cancer Cell Line Encyclopedia (CCLE). Methods: To determine the expression profile and clinical correlations of PD-L1 in lung cancers we used publicly available lung adenocarcinoma and squamous cell carcinoma (SCC) data from TCGA, and small cell and NSCLC line data from the CCLE. We performed Kaplan-Meier and correlation analyses to show how PD-L1 expression correlates with overall survival and other clinical variables. Lung cancer and normal tissue expression comparisons were also performed using normal tissue expressions from the Genotype-Tissue Expression (GTEX) project. Results: Results: PD-L1 mRNA expression from RNA sequencing was available for 517 lung adenocarcinoma and 501 lung SCC samples in the TCGA. The CCLE database contained PD-L1 expression for 12 small cell and 75 NSCLC cell lines. Lung cancers demonstrated a higher PD-L1 expression than most other cancers and normal tissues, and we found that PD-L1 expression was significantly higher in SCC than in adenocarcinoma (p<0.001). Furthermore, PD-L1 showed a significantly higher expression level in pathologic stage II SCC compared to stages I, II, and IV (p<0.05, p<0.05, p<0.01, respectively). Interestingly, stage IV was associated with a lower PD-L1 expression compared to stages I, II, and III (p<0.001). We did not identify similar expression associations with pathologic stage in adenocarcinoma. However, we found that current and also reformed smokers for less than 25 years had a higher PD-L1 expression in adenocarcinoma (p<0.05), but not in SCC. PD-L1 expression was not significantly associated with a survival difference in any stage or histology subgroups. Using the CCLE data we found that NSCLC cell lines showed various expression of PD-L1 that is significantly higher compared to lung small cell carcinoma (p<0.001). Conclusion: The value of PD-L1 expression based on mRNA sequencing in predicting survival in anti-PD-1 naive patients appears to be limited. However, the levels of PD-L1 expression in various disease stages and subgroups of lung cancer patients provide rational for neoadjuvant or window-of-opportunity immunotherapy trials, which would enable us to sort out the mechanisms and to identify patients best suited for immunotherapy.

Keywords: PD-L1, mRNA, survival, TCGA

S426
P2.01-055 LYMPHOCYTES’ SUBTYPES DIFFERENTIATION AFTER STIMULATION WITH SYNTHETIC ANTIGEN-PULSED DENDRITIC CELLS IN LUNG ADENOCARCINOMA PATIENTS
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Department of Pneumology, Oncology and Allergology, Medical University, Lublin/Poland

Background: Immunotherapy in lung cancer is currently experiencing huge interest. The greatest efficacy demonstrated the antibodies against immune checkpoints (PD-1/PD-L1, CTLA-4 or LAG-3). However, an effective anti-tumor response also required tumor antigen presentation to lymphocytes in peripheral lymph nodes. To enhance this effect, vaccination with synthetic tumor antigen was conducted in many clinical trials using antigen presenting cells (APC). Unfortunately, this type of active immunotherapy has not achieved spectacular success (START or MAGRIT studies). The explanation could lie in distorted presentation of tumor antigens in peripheral lymph nodes or in activation of lymphocytes with strong immunosuppressive properties. In our study, we checked which pathways of T helper cells stimulated with synthetic tumor antigens (DCs) after synthetic tumor antigens stimulation. Methods: Peripheral blood was acquired from twenty unseparable and treatment-naive lung adenocarcinoma patients. Using CD14 magnetic beads, two cell populations were isolated. CD14-negative cells were used for CD3-positive cells isolation, which were frozen until further stimulation. CD3-positive cells were cultured in Cell shrink medium supplemented with IL-4 and GM-CSF. After TNF activation, mature DCs were incubated with tumour-specific antigens: MUC1, MAGE-A3, EGFR and CMV (positive stimulator) or only with medium (negative control). Flow cytometry and specific monoclonal antibodies were used to analyze immunophenotypic changes of DCs: CD1a, CD1d, CD2, CD80, CD86, B7-1, B7-2, B7-DC (PD-L2). Mature autologous DCs were cultured with fraction of CD3-positive cells and after 48h of mixed cultures, the expression of intracellular factors specific for different T helper cells subset (T-bet – Th1, STAT-6 – Th2, ROR γt – Th17, FoxP3 – Treg) and expression of extracellular interleukin receptors (IL-12R, IL-4R, IL-23R, TGF-br, IL-2R) were analyzed. Results: Autologous DCs were well generated and showed phenotype specific for fully-mature DCs. In culture with DCs after MUC1 stimulation, we observed in lymphocytes the highest expression of ROR γt and IL-23R (p<0.05) compared with lymphocytes from cultures with other synthetic tumor antigens. Expression of IL-4R on lymphocytes was also significantly (p<0.05) higher in the culture stimulated with MUC1. The highest expression of intracellular FoxP3 factors, TGF-br (p<0.05) and IL-2R (p<0.009) on Th cells were observed in mixed culture with DCs after MAGE-A3 stimulation. Conclusion: Dendritic cells stimulation with synthetic tumor antigens could activate different T helper cell populations. It could depend on the nature of antigens and could influence the effectiveness of stimulation different lymphocyte subtypes in peripheral lymph nodes. Therefore, our study clarifies some failure reasons of large clinical trials using active antigen-specific immunotherapy.

Keywords: dendritic cells, active immunotherapy, tumor antigen, lymphocytes differentiation

POSTER SESSION 2 – P2.01 BIOLOGY/PATHOLOGY IMMUNE MECHANISMS IN THORACIC CANCER AND TARGETED THERAPY – TUESDAY, DECEMBER 6, 2016

P2.01-056 DISTINCT PD-L1 EXPRESSION IN DIFFERENT COMPONENTS OF PULMONARY SARCOMATOID CARCINOMA AND ITS ASSOCIATION WITH MET MUTATION
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Background: Pulmonary Sarcomatoid Carcinoma (PSC) is a unique and highly aggressive subtype of non-small cell lung cancer (NSCLC), characterized by a component of sarcoma or sarcoma-like differentiation. It is generally resistant to platinum-based chemotherapy. However, frequent KRAS and the MET exon 16 skipping mutations have been reported in this subtype. Recently, immunotherapy with antibodies against PD-1/PD-L1 has led to clinical benefits in managing NSCLC. Immune biomarker expression of PD-L1 in differential components of PSC and its relationship with other molecular markers has not been defined and thus there is critical need to investigate its expression profile in this deadly disease. Methods: We investigated PD-L1 expression by immunohistochemistry (IHC) using tissue microarrays from a cohort of 61 patients with PSC (antibody: PD-L1/CD274 (SPH42)). Positive cases were defined as PD-L1+ ≥1%. The clinical and molecular characterization of these cases was previously reported (PMID: 26215952). Among the 41 cases, 36 had sufficient tumor tissue for PD-L1 assessment, 8 (20%) were identified with MET exon 14 skipping mutation and 6 (15%) were found to have KRAS mutations. Results: The PD-L1 expression was positive in 75% (27/36) of cases. Among the positive cases, 78% expressed PD-L1+ ≥50%, whereas 22% had PD-L1 staining of 1-49%. Interestingly, only 33% (9/27) had PD-L1 expression in both epithelial and sarcomatoid components, whereas the remaining 66% detected PD-L1+ in just one component. The PD-L1 expression was statistically different between the two components (P=0.007). Moreover, all 8 patients with MET exon 14 skipping mutation were PD-L1+ positive (6 with PD-L1+ ≥50%), whereas 5 of 6 patients with KRAS mutation expressed PD-L1 (2 with PD-L1+ ≥50%). The average age at diagnosis was similar between the PD-L1 positive vs. negative groups (71 years). There was a trend of shorter overall survival in patients whose tumors were positive for PD-L1 (671 vs. 985 days). Conclusion: In our particular cohort of PSC patients, high PD-L1 (≥50%) was expressed in the large majority of cases which favors potential application of immunotherapy in this disease. In addition, it appears that the expression of PD-L1 is different in the epithelial and sarcomatoid components which could affect scoring in practice. Furthermore, the overall positivity of PD-L1 expression in the unique molecular subtype of PSC patients with MET exon 14 skipping mutation indicates potential interplay between the two biomarkers and suggests that exploration of combination MET and immunotherapy in this subtype is warranted.

Keywords: immune biomarkers, Non Small Cell Lung Carcinoma, PD-L1, MET

POSTER SESSION 2 – P2.01 BIOLOGY/PATHOLOGY IMMUNE MECHANISMS IN THORACIC CANCER AND TARGETED THERAPY – TUESDAY, DECEMBER 6, 2016

P2.01-057 ASSOCIATION OF TUMOR INFILTRATING LYMPHOCYTES QUANTIFICATION WITH EGF-R MUTATIONS IN COMPLETELY RESECTED STAGE IIIA(N2) LUNG ADENOCARCINOMA
Wen Feng1, Xiaolong Fu1, Xuewei Cai2, Qin Zhang3, Yuan Li4, Lei Shen5
1Radiation Oncology, Shanghai Chest Hospital, Shanghai jiao Tong University, Shanghai/China, 2Department of Pathology, Fudan University Shanghai Cancer Center, Shanghai/China

Background: Accumulating data suggests that the extent of lymphocytic infiltrations into the tumor provides prognostic value in non-small cell lung cancer (NSCLC). However, the factors that influence the status of tumor immune environment remain poorly defined and need investigation. The aim of this study was to assess whether the density of tumor infiltrating lymphocytes (TILs) was related to tumor molecular characteristics in completely resected stage IIIA(N2) pulmonary adenocarcinomas, which had undergone complete resection in our hospital between 2005 and 2012. Patients who received neoadjuvant chemotherapy and/or radiotherapy were excluded. DNA of EGFR and KRAS was extracted and purified from paraffin-embedded primary lung cancer tissues samples. EGFR (exons 18, 19, 21) and KRAS (exon 2) mutations analysis were performed by the DNA sequencing. The density of TILs was evaluated by full-face hematoxylin- and eosin-stained sections from surgical specimens for each case by two specialized pathologists. The degree of lymphocyte infiltration into the tumor was scored as none, low, moderate, or high. Patients were stratified into TIL- (none to low infiltration) or TIL+ (moderate to high infiltration) group based on pathologic evaluation. We investigated the association of densities of TILs with tumor-cell mutation status. Results: Among the 192 eligible patients included, 96 (50%) patients were male and 123 (64%) were never/light ex-smokers, and the median age of all patients was 59 years (range, 22–84 years). There were 84 (43.8%) EGFR mutated and 21 (10.9%) KRAS mutated cases. Among the 84 patients with activating EGFR mutations, there were 30 patients harboring mutations in the exon 19 deletions, 35 patients in the exon 21 L858R mutations, and 1 patient with concurrent exon 19 deletion and L858R mutation. The proportion of patients who had higher density of TILs (TIL+) was lower in the EGFR mutation-positive group (42.9% versus 53.7%, P=0.14) and this difference was significantly observed in the patients with L858R mutation and/or exon 19 deletion subgroup (P=0.026). The proportion of patients who had higher density of TILs (TIL+) was significantly lower in the patients harboring L858R mutation and/or exon 19 deletion (37.9% versus 54.8%, P=0.026). Conclusion: There existed association between the lower density of TILs and activating EGFR mutation status in lung adenocarcinoma, underlying the interactions between cancer cells and their microenvironment. Further studies are warranted to validate these results and clarify the potential molecular mechanisms responsible for regulation of lymphocytic infiltration by activating EGFR pathway.

Keywords: lymphocytic infiltration, lung adenocarcinoma, EGFR mutation

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Abstracts

POSTER SESSION 2 – P2.01: BIOLOGY/PATHOLOGY
IMMUNE MECHANISMS IN THORACIC CANCER AND TARGETED THERAPY – TUESDAY, DECEMBER 6, 2016

P2.01-058 MUTATIONAL FEATURES ASSOCIATED WITH IMMUNOREACTIVITY IN NON-CELL LUNG CANCER
Nicholas Syn1, Darwin Tay2, Mohd Feroz Mohd Omar3, Jing Xin Teo4, Joey Lim4, Ross Soo4, Richie Soong2
1Department of Haematology-Oncology, National University Cancer Institute, Singapore/Singapore; 2Cancer Science Institute of Singapore, Singapore/Singapore

Background: Recent reports convey that the abundance and patterns of DNA mutational features in human cancers could modulate their antigenicity and sensitivity to immune checkpoint blockade. We thus sought to comprehensively characterise the immunogenomic landscape of NSCLC. Methods: We used publicly-available molecular (DNA mutation and RNA expression profiles) and clinical data of 658 NSCLC patients from The Cancer Genome Atlas project. HLA-typed was inferred using POLYSOLVER, and we identified neoantigens with patient-specific HLA-binding affinity of IC50<500nM using NetMHC. The relative tumour infiltration by 22 immune cell types was enumerated using CIBERSORT. Finally, we developed and applied MUTPROFILER, a computational approach for mutational signature analysis capable of decoding sequence alterations across 96 trinucleotide contexts. Results: Alterations of immune cell infiltration were observed (Spearman ρ=0.78, P=1.37×10-5), and identified several novel and powerful immunogenomic associations in NSCLC. For instance, the proportion of activated natural killer (NK) cells was greater tumours which showed a higher abundance of 1-3bp insertion/deletions (indels; ρ>0.23, P=1.34×10-5). Furthermore, small (1bp) indels were associated with increased expression of markers of immune cytolytic activity, including TNPα (TNFa; ρ=0.30, P=4.77×10-8) and PDL1 (P=0.15, P=9.12×10-14) and PDCD1LG2 (P=0.21, P=9.12×10-14). Fourteen trinucleotide alterations, including GCA>GTA, TCG>TAG and PDCD1LG2, were stronger correlated with PDCD1LG2 (PD-L2) expression compared to small indels (q>0.10, Fisher’s Z transformation). Interestingly, the number of small frameshifting indels was associated with downregulation of the antigen-presenting machinery (APM) such as TAPI (P=0.22, P=7.93×10-5) and TAP2 (P=0.23, P=1.69×10-7), suggesting a potential immunododging mechanism by which NSCLC tumours co-opt APM pathways to prevent neoantigen-recognition. Finally, by analysing the mutational signatures of the AID/APOBE family, which has important roles in adaptive and innate immunity, we identified a potential novel mutagenic contribution of APOBEC3H, whose expression levels was associated with a pattern of C>A (P=0.18, P=4.76×10-9) and G>C (P=0.14, P=3.67×10-12) within T/C motifs (with the mutated base underlined). Conclusion: Our study portrays an atlas of immunogenetic features in NSCLC. The results sheds light on the dynamics of tumour immune cell infiltration that is likely to form the downstream force behind the clinical activity of novel immunologic strategies, and may lead to new biomarkers and targets for cancer immunotherapy.

Keywords: Immunotherapy, Mutational signatures, Immunogenetics, Immunogenomics

POSTER SESSION 2 – P2.01: BIOLOGY/PATHOLOGY
IMMUNE MECHANISMS IN THORACIC CANCER AND TARGETED THERAPY – TUESDAY, DECEMBER 6, 2016

P2.01-060 COMPARATIVE ANALYSIS OF PD-L1 EXPRESSION BETWEEN CIRCULATING TUMOR CELLS AND TUMOR TISSUES IN PATIENTS WITH LUNG CANCER
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Background: Blockade of programmed death receptor-1 (PD-1) pathway has been shown to be effective against solid tumors including lung cancer. Although PD-ligand 1 (PD-L1) expression on tumor tissue is expected as a potential predictive biomarker, its detection remains challenging due to its dynamic and unstable status. Here, we evaluated the PD-L1 expression on circulating tumor cells (CTCs) in patients with lung cancer and investigated its concordance with that on tumor tissues. Methods: CTCs were captured and immune-stained using microarray system. CTCs were defined as those positive for Cds1 and cytokeratin (CK) and negative for CD45. PD-L1 expression on CTCs were evaluated by addition of the process of PD-L1 immunocytochemistry. For CTCs detection, 0.5 ml of peripheral whole blood was collected from the patients who consented in written form and PD-L1 immunochemistry was performed using corresponding tumor tissues. Results: Sixty-seven lung cancer patients were enrolled in the study between July 2015 and April 2016 at Wakayama Medical University. Patient characteristics were as follows: median age 71 (range, 39 to 86); male 72%; stage II-II/IV; 15/85%; non-small cell lung cancer (NSCLC)/small cell lung cancer (SCLC)/Other, 73/21/6%. CTCs were detected in 66 out of 67 patients (median 19; range, 0 to 115) and more than 5 CTCs were detected in 78% of patients. PD-L1 expression on CTCs were detected in 73% of patients and the proportion score (PS) of PD-L1 expression on CTCs ranged from 3% to 100%. The intra-patient heterogeneity of PD-L1 expression on CTCs. Significantly more PD-L1 expressing CTCs were detected in patients without EGFR mutations than those with EGFR mutations (P=0.0338). Tumor tissues were available from 27 patients and were immune-stained for PD-L1. No positive correlation was observed on PD-L1 expression between tumor tissues and CTCs based on PS (R²=0.0103). Three adenocarcinoma cases with PD-L1-positive tumor tissue did not harbor any PD-L1 expressing CTCs and conversely, three adenocarcinoma cases with PD-L1-negative tumor tissue harbored PD-L1 expressing CTCs. The total concordance between tumor tissues and CTCs was 19%. It is also noteworthy that SCLC patients had perfect agreement on PD-L1 expression between tumor tissues and CTCs. Conclusion: PD-L1 expression was detectable on CTCs in lung cancer patients and intra-patient heterogeneity of its expression was observed. There was no agreement between tumor tissues and CTCs. Further investigation is warranted to better understand the clinical significance of PD-L1 expressing CTCs.

Keywords: Circulating tumor cells, PD-L1, liquid biopsy, PD-1

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Background: The understanding of the co-expression of immune checkpoints in non-small cell lung carcinoma (NSCLC) is important to potentially design combinatorial immunotherapy approaches in this disease. We examined the expression of a panel of immune checkpoints markers by immunohistochemistry (IHC) and quantitative image analysis in a large cohort examined the expression of a panel of immune checkpoints markers by immunohistochemistry (IHC) and quantitative image analysis in a large cohort of formalin fixed and paraffin embedded (FFPE) tumor tissues from stage I-III NSCLCs, including molecular characteristics. Methods: We studied 225 formalin fixed and paraffin embedded (FFPE) tumor tissues from stage I-III NSCLCs, including molecular characteristics. We focused on 13 adenocarcinomas (ADC) and 83 squamous cell carcinomas (SCC), placed in tissue microarrays (TMA samples). Nine immune checkpoint markers, 4 (PD-L1, B7-H3, B7-H4, IDO1) expressed predominantly in malignant cells (MCs), and 5 (ICOS, VISTA, TIM3, LAG3 and OX40) expressed mostly in stromal tumor infiltrating lymphocytes (TAICs). All IHC markers were examined using quantitative image analysis system (Aperio). Results: Using > median value of the immune checkpoint expression as positive the immunohistochemical expression was observed that MCs H-score expression of PD-L1, B7-H3, B7-H4 and IDO1 was higher in ADC than SCC, with 3 out of 5 markers demonstrating statistically significant differences. Furthermore, we identified frequent expression of markers: a) 11% ADC (5/123) and 10% SCC (8/83) co-expressed 6 to 7 markers, c) 28% ADC (35/123) and 40% SCC (33/83) co-expressed 6 to 7 markers, d) 16% ADC (20/123) and 18% SCC (15/83) co-expressed 2 to 3 markers, e) 12% ADC (15/123) and 18% SCC (15/83) co-expressed 4 to 5 markers, and f) 12% ADC (15/123) and 18% SCC (15/83) co-expressed 4 to 5 markers. In ADC, high expression of TAICs expressing OX40 and Id4 levels of MCs expressing B7-H4 were detected in tumors with EGFR (median, 74.9 vs. 1.6, P = 0.021) and KRAS (median, 6.88 vs. 0.67, P = 0.033) mutation compared with wild-type tumors, respectively. Univariate analysis demonstrated that high B7-H4 and low OX40 expression in MCs in a frequent event in ADC patients. Conclusion: We detected different patterns of immune checkpoints expression in NSCLC with higher level of markers found in malignant cells of SCC and in stromal inflammatory cells of ADC. Immune checkpoints expression correlated with the outcome of NSCLC patients. Importantly, co-expression of several immune checkpoints is a frequent event in NSCLC (Supported by CPRIT MIRA and UT Lung SPARE grants). Keywords: Image Analysis-based, Immune checkpoints, Tissue Microarrays, Non-small cell lung carcinoma.

Background: The number and function of tumor infiltrating lymphocytes (TILs) represent an important prognostic factor in cancer. Among the multiple immune escape mechanisms triggered by cancer, the PD-1/PD-L1 checkpoint seems to play a central role. Accordingly, PD-1/PD-L1 inhibitors have shown significant clinical results in multiresistant NSCLC. However, the role of this immune checkpoint on tumor biology and clinical outcome remains to be determined. To this end, the number and distribution of subpopulations of TILs together with the quantification of PD-L1 expression were immunohistochemically assessed in NSCLC and their impact on patients survival evaluated. Methods: Histologic sections from 106 NSCLC (46 ADC, 60 SCC) were morphometrically analysed after immunohistochemical assessment of the incidence of CD3+, CD8+ and PD-1+ TILs and their proximal or distal location with respect to a neoplastic cell, as well as the expression of PD-L1 on TILs and cancer cells. Results: We showed that high B7-H4 and low OX40 expression in MCs and in TAICs respectively that high B7-H4 and low OX40 expression in MCs and in TAICs respectively with wild-type tumors, respectively. Univariate analysis demonstrated that high B7-H4 and low OX40 expression in MCs in a frequent event in ADC patients. Conclusion: We detected different patterns of immune checkpoints expression in NSCLC with higher level of markers found in malignant cells of SCC and in stromal inflammatory cells of ADC. Immune checkpoints expression correlated with the outcome of NSCLC patients. Importantly, co-expression of several immune checkpoints is a frequent event in NSCLC (Supported by CPRIT MIRA and UT Lung SPARE grants). Keywords: Image Analysis-based, Immune checkpoints, Tissue Microarrays, Non-small cell lung carcinoma.
POSTER SESSION 2 – P2.01: BIOLOGY/PATHOLOGY IMMUNE MECHANISMS IN THORACIC CANCER AND TARGETED THERAPY – TUESDAY, DECEMBER 6, 2016

P2.01-064 MOLECULAR CONTEXT OF IMMUNE MICROENVIRONMENT IN EARLY-STAGE LUNG SQAMOUS CELL CARCINOMA

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Background: Although it has been proposed that the number of somatic mutations, together with high PD-L1 and CD8 expression, defines a type of tumor microenvironment predictive of response to immune checkpoint inhibitors, this data has been challenged because the methodologies are difficult to reproduce (e.g. tissue microarrays, whole exome sequencing or complicated scoring approaches). This situation prompted us to investigate possible alternatives that are easier to reconcile with daily practice. Methods: A total of 40 consecutive patients with early stage lung squamous cell carcinoma who underwent surgery at HM Sanchinarro University Hospital were considered. Automated immunohistochemistry (IHC) for PD-L1 expression was performed on whole tissue sections (Benchmark ULTRA, OptiView, Ventana Medical Systems, USA) with three different antibodies: SP142 (Ventana), SP263 (Ventana), and EIL3N (Cell Signaling). PD-L1 IHC was considered positive according to the criteria used in the corresponding clinical trials. P53 aberrant IHC expression was used as a surrogate marker for TP53 mutations. Whole tissue sections were also automatically scored for CD8+ tumour-infiltrating lymphocytes (TILs) density (off-label algorithm on the iScan Core). Afterwards, we performed targeted next-generation sequencing (NGS) of 52 genes (Oncomine Focus Assay) 1, 2. Life Technologies, USA). The prognostic impact of all these variables was also evaluated. Results: Correlation between EIL3N and SP142 or SP263 was similar when scoring tumour cells (Tcs) (0.94). There was a significant association between the intraepithelial and peritumour stromal CD8+ TILs density and overall survival when using the image analysis software (p<0.032). The presence of ≥47 CD8+ cells/mm² had a 94% specificity and a 67% sensitivity for identifying patients with at least 5% SP142 PD-L1+ Tcs. The highest percentage of PD-L1+ Tcs were found in samples with CD68 (2.6%) or MYC (2.6%) amplifications. Cases with FGFR1 amplification (7.9%) were negative for all PD-L1 antibodies. P53 aberrant expression and PD-L1 expression in Tcs also seem to be related. Conclusion: The methodology presented herein could help align the use of targeted NGS and the immune microenvironment assessment to increase the clinical value of immune checkpoint inhibitors. Acknowledgements: This study was partially funded by Instituto de Salud Carlos III (ISCIII), Fondo de Investigaciones Sanitarias (FIS), Fondos FEDER-Plan Estatal de I+D+i (2013-2016, PI14-0176).

Keywords: NGS, Squamous cell carcinoma, PD-L1, CD8

POSTER SESSION 2 – P2.01: BIOLOGY/PATHOLOGY IMMUNE MECHANISMS IN THORACIC CANCER AND TARGETED THERAPY – TUESDAY, DECEMBER 6, 2016

P2.01-065 QUANTIFICATION OF TUMOUR-IMMUNE CELL SPATIAL RELATIONSHIPS IN THE LUNG TUMOUR MICROENVIRONMENT USING SINGLE CELL PROFILING

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Background: How clinical-genomic features of the lung tumour microenvironment (TME) influence immune-checkpoint-blockade therapy is not well understood. Immunohistochemistry (IHC) is necessary to decipher cell-cell relationships that cannot be observed by bulk tumour profiling. In this pilot study, we assess whether immune cell phenotypes and spatial relationships differ between lung adenocarcinoma (LUAD) from smokers/non-smokers, KRAS/EGFR mutation, or with stage and tumour size using a novel multicolour IHC quantitative pathology method that enables in situ single cell profiling within the TME. Methods: Two consecutive sections from 21 cases of LUAD were stained with multicolour IHC panels to assess immune cell composition (CD8, CD3, CD79a) and T-cell exhaustion (CD8, PD1). Hyperspectral images were captured as directed by a pathologist and analyzed using software developed in-house. The software segments individual cell boundaries based on haematoxylin stain. IHC stain positivity thresholds were applied based on intensity. Tumour and immune cells were classified into groups based on IHC staining. Interactions between specific groups were quantified by assessing the frequency and variance of the spatial relationship of each group vs. all other groups. Voronoi tessellation, based on cell centres, was used to define “next to”. Group counts and relationships were then compared with clinical features using a Student’s t-test or Kruskal-Wallis test. Results: A greater number of cells expressed PDL1 in KRAS+ LUAD. While the total number of CD8+PD1+ T-cells did not differ between KRAS+ and EGFR+ LUAD, there was an observed increased proximity between PD-L1+ cells and CD8+PD1+ T-cells in KRAS+ LUAD. In EGFR+ LUAD, CD8+ T-cells that did not express PD1 were primarily localized in PD-L1 negative regions. Both EGFR LUAD and never smokers harbored a higher proportion of CD8+ T-cells and CD3+CD8+ immune cells. Both immune cell types were frequently localized in clusters with CD8+ T-cells. KRAS+ LUAD and smokers had increased B-cell counts. No significant associations of PD1 and PDL1 expression were found with stage, however, there was a statistically significant increase in proximity between varied immune cell types as stage and tumour size increased. Conclusion: Our method enabled identification of specific cell-cell spatial relationships within LUAD that are associated with smoking history and KRAS/EGFR mutation. Despite limited sample size, we observed an increased proximity between PD-L1+ cells and CD8+PD1+ T-cells in patients with lung squamous cell carcinoma. Single cell profiling and cell sociology is a promising method to improve stratification of patients for immune-checkpoint-blockade therapies and opens new avenues to explore the complex cell-cell interactions within the TME.

Keywords: single cell profiling, quantitative pathology, Immunology, tumour microenvironment

POSTER SESSION 2 – P2.01: BIOLOGY/PATHOLOGY IMMUNE MECHANISMS IN THORACIC CANCER AND TARGETED THERAPY – TUESDAY, DECEMBER 6, 2016

P2.01-066 PD-L1 TUMOR EXPRESSION AND ITS EFFECT ON OVERALL SURVIVAL AMONG PATIENTS WITH RESECTED NON-SMALL-CELL LUNG CANCER (NSCLC)

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Background: Anti-PD1 monoclonal antibodies have demonstrated survival advantage over conventional chemotherapy in progressive metastatic non-small cell lung cancer (NSCLC). The prognostic role of tumour expression of PD-L1 in NSCLC remains conflicting. We performed this study to evaluate the impact of PD-L1 expression as a prognostic marker in non-metastatic NSCLC. Methods: NSCLC patients (pts) who underwent curative resection between 1998 and 2006 in St James’ Hospital, Dublin were included. PD-L1 status was assessed using Ventana SP124 antibody on archival FFPE surgical tumour specimens, arrayed on tissue microarrays (TMAs) with triplicate 0.6 mm cores. PD-L1 was scored as positive if membranous staining was present in ≥1% of tumour cells aggregated across the replicate cores to address heterogeneity. Clinical characteristics of the pts were obtained from the hospital electronic database including age, gender, histological subtype, smoking status, grade, tumour size, nodal status, stage at diagnosis, and survival data. Results: One-hundred and forty-seven patients from our institutional database were included, of which 92 (63.0%) were males, with a median age of 65 years (range: 42-82). 53.1%...
Background: The communication between epithelial cells and their underlying stroma is an important but poorly understood aspect of organismal biology. If aberrantly regulated, these interactions can prove to be tumorigenic. Although it has been known for years that cancer-associated fibroblasts (CAF's) promote and sustain the growth of tumors, the underlying mechanisms remain incompletely understood. Previous work in our lab has identified a novel mechanism of communication in which CAFs secrete cardiophorin-like cytokine factor 1 (CLCF1), a cytokine that binds ciliary neurotrophic factor receptor (CNTFR) on tumor cells and promotes neoplastic growth. CNTFR is a component of the tripartite receptor complex formed by CNTFR-gp130-LIFR and is capable of activating several oncogenic signaling cascades, including JAK-STAT, MEK-ERK. Using xenograft models, we found that CLCF1 overexpression by CAFs increases tumor growth while knockdown of CNTFR in lung tumor cells decreases overall growth. With the use of advanced protein engineering technology, we generated a high-affinity CNTFR decoy that inhibits CLCF1-CNTFR signaling and are currently testing this novel reagent to elucidate the mechanism by which CNTFR activation alters intercellular signaling to increase tumor cell growth. In vivo studies with cell lines and PDx models, we are also exploring the efficacy of this CNTFR decoy as a mechanism of lung cancer therapy. Conclusion: In sum, these data indicate that CLCF1-CNTFR signaling is important for NSCLC tumor growth and is a viable therapeutic target.

Keywords: NLF, CLCF1, CAF, CNTFR
Abstracts

POSTER SESSION 2 - P2.01: BIOLOGY/PATHOLOGY
MARKER FOR PROGNOSIS, PREDICTION – TUESDAY, DECEMBER 6, 2016

P2.01-070 CIRCULATING BIOMARKERS OF FRAILTY ARE ASSOCIATED WITH A POOR PROGNOSIS IN PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC)
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Background: Patients with borderline performance status (PS), multiple co-morbidities or who are frail have increased chemotherapy toxicity. With an ageing population, more NSCLC patients are presenting with these characteristics. Improved assessment is required to distinguish those patients likely to benefit from therapy from those where treatment precipitates significant functional decline. The Newcastle 85+ study identified circulating biomarkers associated with frailty in a cross-section of adults aged 85 years (n=845). Their utility in NSCLC is not known. Methods: Samples from 161 patients (median age 65; range 33 to 81) with advanced NSCLC (stage 3B/4) and PS adequate to consider systemic therapy (34% PS0; 53% PS1; 13% PS2) were analysed for biomarkers of frailty at Northern Institute for Cancer Research and Newcastle Institute for Ageing, Newcastle University, Newcastle UK. Biomarkers included telomere length, adiponectin, high sensitivity CRP (hsCRP), IGFBP1, TGF-β, Alpha-1 acid Glycoprotein (AAG) and FLT3 ligand. Full blood count, liver function tests, serum creatinine, CR-51 EDTA glomerular filtration rate and survival were extracted from patients’ clinical notes. Results: Age and line of therapy were not predictive of survival. As expected PS 2 was associated with significantly worse survival (70 days vs 315 days (PS 0, p=0.0001) and was associated with significantly higher biomarkers of inflammation (high hsCRP, AAG, TGF-β and neutrophils, low albumin and haemoglobin). In PS 0-1 patient’s high hsCRP, shorter telomere length and low adiponectin were associated with poor survival. An exploratory risk score combining biomarkers was a stronger predictor of prognosis than PS alone (Figure 1). HR 3.2 (95%CI, 2.0 to 5.2), p<0.0001, and seemed to be particularly useful in patients >65years; HR 4.1 (95%CI, 2.0 to 8.4), p<0.0001.

Keywords: frailty, chemotherapy, Biomarkers

POSTER SESSION 2 - P2.01: BIOLOGY/PATHOLOGY
MARKER FOR PROGNOSIS, PREDICTION – TUESDAY, DECEMBER 6, 2016

P2.01-071 BIOLOGICAL IMPLICATION OF CYTOPLASMIC ECT2 IN MALIGNANT PROGRESSION OF LUNG ADENOCARCINOMA
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Background: Epithelial cell transforming 2 (ECT2) is a guanine nucleotide exchange factor (GEF) for Rho family GTPases including RhoA, Rac, and Cdc42. In normal cells, ECT2 is found primarily in the nucleus, whereas it regulates dynamic processes including the cell cycle and cytokinesis. On the other hand, several studies have suggested that ECT2 signaling promotes tumor proliferation, migration, and invasion in non-small cell lung cancer. Recently, Murata et al. demonstrated that ECT2 is amplified in early invasive adenocarcinoma but not in situ adenocarcinoma (Cancer Sci, 105:690, 2014). However, the oncogenic mechanism whereby ECT2 drives cell transformation in lung adenocarcinoma is still unknown. Methods: Cellular fractionation assay was conducted using nine lung adenocarcinoma cell lines Calu-3, A549, H1650, PC-9, H123, H1975, LC-29, and HCC827. Immunoblotting, Immunofluorescence, and Immunohistochemistry assays were used to evaluate the expression and localization of ECT2. For ECT2 amplification, nine lung adenocarcinoma were genetically examined using Quantitative Real-Time PCR. Immunoprecipitation was used to examine the interaction between ECT2 and PKC. And ECT2-SRNA was confirmed the effect of ECT2 on the downstream signaling pathway. Results: In this study, we showed that ECT2 was localized predominantly in the nucleus of normal lung epithelial cells, whereas tumor cells in nine lung adenocarcinoma cell lines expressed ECT2 protein to differing degrees in their cytoplasm. Importantly, high expression of cytoplasmic ECT2 in surgically resected materials was significantly associated with poor outcome. Moreover, our data showed that overexpression of ECT2 mRNA was roughly correlated with ECT2 amplification in lung adenocarcinoma cell lines. We then investigated the mechanism underlying the cytoplasmic localization of ECT2 and its oncogenic activity in lung adenocarcinoma using the lung adenocarcinoma cell lines Calu-3, A549, H1650, PC-9, H123, H1975, LC-29, and HCC827. We found that the cytoplasmic ECT2 was phosphorylated and bound to protein kinase Cota (PKCα) in the cytoplasm. We also observed that the overexpression of cytoplasmic ECT2 greatly increased its degree of phosphorylation and enhanced its interaction with PKCα, resulting in significant promotion of tumor growth through activation of the MEK1/2/Erk1,2 cytoplasmic downstream signaling pathway. Conclusion: These results indicate that aberrant cytoplasmic localization of ECT2 is a specific feature of lung adenocarcinoma and important for its malignant progression. This finding offers new insight into the molecular mechanism responsible for aberrant cytoplasmic localization of ECT2, which is correlated with the progression of malignancy, and highlights cytoplasmic ECT2 expression as a new prognostic biomarker in lung adenocarcinoma.

Keywords: Prognostic Biomarker, Progression of Malignancy, Epithelial cell transforming 2 (ECT2), lung adenocarcinoma

POSTER SESSION 2 - P2.01: BIOLOGY/PATHOLOGY
MARKER FOR PROGNOSIS, PREDICTION – TUESDAY, DECEMBER 6, 2016

P2.01-072 CLINICAL ASSOCIATIONS OF MUCI EXPRESSION IN HUMAN LUNG CANCER AND PRECANCEROUS LESIONS
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Background: Mucin 1 (MUC1) is a cell membrane glycoprotein overexpressed in many human cancers, including nonsmall cell lung cancer (NSCLC). Its role has been implicated in carcinogenesis of premalignant lung lesions in animal models and in clinical association with prognosis in NSCLC. Thus, MUC1 has been a target of interest for vaccine strategies as an immunomodulatory approach to lung cancer treatment and prevention.

Keywords: MUC1, Vaccine, Immunomodulatory

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Methods: Tumor samples from 38 patients with biopsy-proven NSCLC were assessed for MUC1 expression as determined by immunohistochemistry, expressed on a 0 to 3 scale. Levels of MUC1 expression in areas of dysplasia, metaplasia, bronchoalveolar carcinoma (BAC) and carcinoma present within the same tissue sample were characterized independently and compared using the paired t-test. Clinical data including patient characteristics, staging, treatment and survival were also assessed for correlation with MUC1 expression. Results: 16 patients with squamous and 19 patients with glandular lesions had tumor samples that were satisfactory for analyses. Among squamous lesions, there was a significant increase in MUC1 expression score in dysplastic compared with metaplastic areas (mean difference = 0.83, 95% CI. 0.21 to infinity; p = 0.021). We also observed an increase in squamous cell carcinoma compared with dysplastic areas (mean difference  = 0.46, 95% CI. 0.06 to infinity; p = 0.052). Among glandular lesions, there was a nonsignificant increase in MUC1 expression in adenocarcinoma compared with BAC (mean difference = 0.20, 95% CI. 0.055 to infinity; p = 0.094). According to the Spearman correlation test (p = 0.020 for biopsy score; p = 0.008 for dysplasia score), a significant positive correlation was observed between MUC1 expression and survival in patients with squamous lesions; however, no significant correlation was observed between MUC1 expression and survival in patients with adenocarcinoma. Conclusion: MUC1 overexpression appears to be increased with the progression of premalignant lung lesions to invasive carcinoma in patients with NSCLC. This supports the rationale for MUC1 as a therapeutic target in tumor vaccines that could be ultimately used to prevent or reverse precancerous lesions and treat lung cancer.

Keywords: MUC1, tumor vaccine, NSCLC, mucin

Poster Session 2 - P.01 BIOLOGY/PATHOLOGY MARKER FOR PROGNOSIS, PREDICTION - Tuesday, December 6, 2016

P2.01-073 THE DIAGNOSTIC VALUE OF CARCINOEMBRYONIC ANTIGEN AND SQUAMOUS CELL ANGINANT IN LUNG ADENOSQUAMOUS CARCINOMA
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Background: Lung adenosquamous carcinoma (ASC) is a rare malignant tumor with an adenocarcinoma and a squamous cell carcinoma component, and associated with a lower 5-year survival rate than lung squamous cell carcinoma and lung adenocarcinoma. Surgical specimen histology revealed inadequacy of conventional transbronchial needle aspiration sample in the diagnosis of lung ASC. Most of lung ASC patients are not suitable to receive surgery, and it is difficult to diagnosis ASC. This study is to explore the possibility of using serum carcinoembryonic antigen (CEA) and squamous cell carcinoma antigen (SCC) as a supplementary diagnostic test for ASC. Methods: We retrospectively analyzed the preoperative serum CEA and SCC levels in 34 patients with lung ASC, 35 cases of lung adenocarcinoma patients, 35 cases of lung squamous cell carcinoma patients. 36 cases of lung benign disease patients and 35 cases of healthy people as control group were also retrospectively collected and analyzed from January 2012 to December 2014 at the Zhejiang Cancer Hospital, China. The differences of CEA and SCC among the groups were evaluated, and the area under the curve (AUC), sensitivity and specificity were calculated. Results: The levels of CEA and SCC in lung ASC group were significantly higher than those in healthy control group and benign disease group (p<0.05), and SCC level in lung ASC group was significantly higher than that in lung adenocarcinoma group (p<0.05). CEA and SCC had good diagnostic sensitivity and specificity compared with the healthy control group, and the difference was statistically significant (p=0.05). Conclusion: Our retrospective study suggested a role for serum CEA and SCC levels as reference markers in the diagnosis of lung ASC. If the patients which CEA and SCC levels were elevated and diagnosed as lung adenocarcinoma by limited biopsy materials should be offered further work-up to reach an accurate diagnosis and treatment.

Keywords: adenosquamous carcinoma, carcinoembryonic antigen, squamous cell carcinoma antigen

Poster Session 2 - P.01 BIOLOGY/PATHOLOGY MARKER FOR PROGNOSIS, PREDICTION - Tuesday, December 6, 2016

P2.01-074 INCREASED AIMP2-DX2/AIMP2 AUTOANTIBODY RATIO IS ASSOCIATED WITH POOR PROGNOSIS IN LUNG CANCER
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Background: Aminoacyl t-RNA synthetase-interacting multi-functional proteins (AIMPs) are scaffolding protein required for the assembly of the 1-tRNA synthetase complex, forming multisynthetase complex. Besides their inherent roles, AIMPs translocate to the other cellular compartments and involve in various cellular pathways. On the other hands, its alternative spliced form lacking exon 2 (AIMP2-DX2) compromises the tumor suppressive activity of AIMP2. Recently, presence of autoantibodies against AIMP2-DX2 and AIMP2 were identified in human blood but its clinical implication is unknown. Methods: The diagnostic usefulness of blood autoantibody against AIMP2-DX2 and AIMP2 was investigated in 80 lung cancer cases and 11 age, gender and smoking status matched control cases using ROC curve. To exploit their clinical implication, blood level of autoantibody against AIMP2-DX2, AIMP2 and AIMP2-DX2/AIMP2 ratio was analyzed with clinical parameters in 165 lung cancer patients. Results: There was no statistically significant difference in the blood autoantibody level against AIMP2-DX2 and AIMP2 between lung cancer and control cases. However AIMP2-DX2/AIMP2 ratio was higher in lung cancer patients (30.7±12.6 vs. 39.1±8.4, P=0.001, 1-test). When their diagnostic usefulness was evaluated by ROC curve generation, the AUC of auto-antibody level of AIMP2-DX2, AIMP2, and AIMP2-DX2/AIMP2 ratio were 0.416, 0.579 and 0.357 respectively, suggesting their diagnostic value in lung cancer is limited. At total 165 lung cancer patients were classified into 2 groups, high and low group, on the basis of median value of AIMP2-DX2, AIMP2, and AIMP2-DX2/AIMP2 ratio, respectively, then further analyzed. There was no statistical difference in the gender, smoking, pathologic diagnosis and stage between high and low group of AIMP2-DX2, AIMP2, and AIMP2-DX2/AIMP2 ratio. But AIMP2-DX2 high group was older than those with lower AIMP2-DX2 group (66.8±8.4 vs. 63.8±10.3 years, P-value=0.040, t-test). When the relationship with CEAS and CYFRA21 was evaluated, the AIMP2-DX2/AIMP2 high group showed higher CYFRA21 level (7.9±12.1 vs. 3.4±3.3 ng/ml, P-value=0.020, t-test). There was no significant relationship between AIMP2-DX2 and AIMP2 concentration with progression free survival and overall survival. But the high levels with high AIMP2-DX2/AIMP2 ratio showed significant short overall survival (18.6 [95% CI. 15.19-22.00] vs. 48.9 [95% CI. 16.89-82.91 months], P-value=0.021, Log-Rank Test). Conclusion: Autoantibodies against AIMP2-DX2 and AIMP2 exist at detectable level in human blood. Increased AIMP2-DX2/AIMP2 ratio is closely related to the poor clinical outcome of lung cancer patients, indicating those are warranted for further study for development as biomarkers in lung cancer.

Keywords: aminoacyl tRNA synthetase complex interacting multi-functional protein 2, lung cancer, alternative spliced form of aminoacyl tRNA synthetase complex interacting multi-functional protein 2, biomarker

Poster Session 2 - P.01 BIOLOGY/PATHOLOGY MARKER FOR PROGNOSIS, PREDICTION - Tuesday, December 6, 2016

P2.01-075 PROGNOSTIC VALUE OF ANGIOGENESIS AND CELL ADHESION BIOMARKERS IN NON-SMALL CELL LUNG CANCER
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Background: Previous data on the prognostic value of vascular endothelial growth factor (VEGF), E-cadherin and CD44 in non-small cell lung cancer (NSCLC) remain limited and largely controversial. The primary aim of this study was to further investigate these proteins, along with other well-studied biomarkers of prognosis, as predictors of overall survival (OS) in NSCLC. Methods: Formalin-fixed, paraffin-embedded tissue samples from 77 surgical and 41 autopsy cases, were retrieved and evaluated by immunohistochemistry (IHC) for the expression of VEGF, E-cadherin, CD44, p53, Ki-67 and thyroid transcription factor-1 (TTF-1). Immunohistochemical findings were correlated with gender, age, primary tumor location/side, tumor histology and grade and disease stage at diagnosis. The association of clinicopathologic variables and IHC results with overall survival (OS) was assessed – only in the surgical subgroup – by univariate and multivariate Cox regression analysis. Results: Mean age of all cases (N=118) was 64.8 years (SD±11.1 years), while the majority were men (104/118, 88.1%). Adenocarcinoma was the predominant histological type (38.1%), while most cases (62.6%) had stage II disease at diagnosis. E-cadherin and CD44 expression were significantly correlated with lower tumor grade and disease stage at diagnosis, both in the total sample and in the surgical and autopsy subgroups. Positive VEGF expression was also correlated with lower grade and stage, in the total sample and the autopsy subgroup, but not in the surgical subset of cases. Positive E-cadherin and CD44 expression were associated with
P2.01-076 DREBRIN: A NEW TARGETABLE MOLECULAR MARKER OF LUNG ADENOCARCINOMA
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Background: Embryonic antigens, such as carcinoembryonic antigen (CEA) and alpha-fetoprotein (AFP), are routinely employed as serum and immunohistochemical tumor markers in clinical medicine. Since they are not expressed in adult human tissues, it is reasonable to conclude that embryonic antigens are extremely specific tumor markers. However, no systematic studies have yet identified clinically useful embryonic antigens for tumor diagnosis. In the present study, we developed a strategy for systematic identification of lung adenocarcinoma markers using monoclonal antibodies generated from embryonic swine tissue. Swine mRNA shows more than 80% homology with human mRNA, and embryonic swine tissue is thought to be a useful material for detection of human embryonic markers. Methods: To produce mouse monoclonal antibodies, we immunized BALB/c mice by injection of fetal swine lung nuclear fraction into the hock, and used a human lung adenocarcinoma nuclear fraction for the second immunization. We recovered lymph nodes from the mice, and fused mouse B lymphocytes with the murine myeloma cell line SP2/0 using polyethylene glycol. The resulting hybridomas were then selectively cultured. For selection of interesting hybridoma clones, we performed immunohistochemical staining using the supernatant from each clone, with tissue microarray loading swine fetal and adult lung, human lung cancer and normal lung tissue. Results: Immunohistochemical studies showed that the antibodies derived from four of them were strongly reactive with the cytoplasm and cytomebrane of fetal swine lung and human lung cancer. We then focused on one clone (B246) whose antibody reacted most clearly with human lung adenocarcinoma cells. Protein microarray analysis confirmed that B246 reacted specifically with "drebrin", one of the actin binding proteins, originally identified in neuronal cells. There are two drebrin isoforms in human tissue: drebrin E (embryonic) is abundant in the developing neurons, and drebrin A (adult) is expressed in adult brain. We then examined the association of the drebrin antibody expression with the pathological features and prognosis of lung adenocarcinoma using 200 selected cases for which formalin-fixed and paraffin-embedded samples were available. Drebrin immunohistochemistry delineated the samples into those with strong (n=85) and weak (n=115) drebrin expression. Kaplan-Meier analysis demonstrated a significant difference in disease-free survival (DFS) between the groups with strong and weak drebrin expression (p=0.033). Conclusion: Drebrin is expressed specifically in lung adenocarcinoma and is associated with outcome. The present findings indicate that drebrin is a new marker of lung adenocarcinoma and indicative of prognosis.

Keywords: drebrin, marker, Prognosis, Adenocarcinoma

P2.01-077 SERUM CYFRA 21-1 AND CEA LEVEL AS A PREDICTING MARKER FOR ADVANCED NON-SMALL CELL LUNG CANCER
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Background: Tumor markers such as CEA and CYFRA 21-1 have been shown to be effective in patients with non-small cell lung cancer as an aid in diagnosis and monitoring response to treatment. CYFRA 21-1 is a fragment of cytokeratin 18, present in the cytoplasm of tumor cells of epithelial origin. CEA or Carcino-Embryonic Antigen is a cell surface protein. Methods: We recruited advanced non-small cell lung cancer patients who received first line treatment with standard chemotherapy between February and September 2015 in Maharaj Nakorn Chiang Mai hospital. Excluded criteria were patients who had history of other active cancers who had end stage renal disease (confounding factors to serum CYFRA measurement). Clinical data was obtained and a blood sample was collected at baseline, after start chemotherapy at cycle 2nd and at the end of treatment. Serum tumor marker levels were determined with a test kit (Roche Diagnostics Corp) using a Cobas e 411 analyzer. Primary objective outcome is correlation in dynamic change of serum CYFRA and CEA level and clinical response from diagnostic assessment. Secondary objective outcome Secondary objective outcome is optimal cut point to predict the treatment outcome from sensitivity and specificity analysis. Statistical Analysis Multivariable logistic regression analysis was used to identify the effect of changed value of CYFRA 21-1 C-statistic was used to identify the optimal cut of point of changed value of CYFRA 21-1 to predict the outcome of treatment demonstrated by area under receiver operating characteristic curve (AUROC). The p-value <0.05 was considered statistically significant. All statistical analysis was performed using STATA program (version 12.0). Results: Forty patients (24 males and 16 females) were enrolled. The median age was 59.8 years. Histology subtypes were adenocarcinoma (70%), squamous cell (22.5%), and large cell carcinoma (5%) and (NOS)(not otherwise specified) (2.5%). The treatment responses were partial response (50%), complete response (27%), and disease progression (22.5%). The result demonstrated significant correlation between dynamic change of serum CYFRA level and clinical benefit from diagnostic assessment. Mean change value of CYFRA 21-1 before and after treatment between clinical benefit group (PR + SD) and PD group were −7.7±9.2 and 12.5±23.2 respectively (p=0.001). In contrast dynamic change of CEA did not show significant correlation. For secondary end point, at cut point of 2 ng/ml reduction of CYFRA level after treatment had the most accepted from AuROC curve. Conclusion: CYFRA 21-1 have capability to predict benefit from treatment from chemotheraphy in non-small cell lung cancer.

Keywords: cyfra21-1 CEA non-small cell lung cancer biomarker

P2.01-078 FREQUENT HIGH TIM-3 (HAVCR2) EXPRESSION IN RESECTED NSCLC SPECIMENS, MOST NOTABLY IN ADENOCARCINOMA HISTOLOGY
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Background: Anti-programmed cell death-1 (PD-1) therapies have produced durable responses in advanced non-small cell lung cancer (NSCLC), but objective response rates in unselected populations remain modest at approximately 20%. As a result, therapies targeting other immune checkpoints are currently being investigated as monotherapy or in combination with anti-PD-1 therapy. One such immune checkpoint is T-cell immunoglobulin and mucin-domain containing 3 (TIM-3), which is involved in T-cell exhaustion and has also been found on NSCLC tumor cells, more frequently in adenocarcinoma. The present study sought to further characterize the expression of TIM-3 in resected NSCLC specimens via microarray analysis. Methods: Gene expression microarray analysis was performed using the Agilent Whole Human Genome 4x4K 2-color platform for 319 NSCLC and 15 normal lung resection specimens. The reference sample was an equal mixture of 258 of the NSCLC samples included in the study. Microarray data was imported into Rosetta Resolver for analysis. Samples with expression significant at greater than the reference level were classified as high, samples with expression unchanged from the reference were classified as moderate, and samples with significantly lower levels were classified as low (P<0.01). Relationships between TIM-3 expression and smoking status, histology, T stage, and gender were evaluated with the chi-square test. The three survival curves based on TIM-3 expression were compared and a single p-value based on chi-square test was determined using Statistica 13.0. Results: Within the 319 NSCLC tissue samples, 90 samples (28%) had high TIM-3 expression, 150 samples (47%) had moderate expression, and 79 samples (25%) had low expression. Interestingly, 47%
(17/15) of normal lung samples evidenced high TIM-3 expression, while none had low TIM-3 expression. Tumors with adenocarcinoma histology had a greater percentage of samples with high TIM-3 expression (34%), compared to those with squamous cell histology, 17% (p=0.03). Gender and T stage were not significantly related to TIM-3 expression level, while a trend towards higher TIM-3 levels was observed in smokers compared to non-smokers (p=0.10).

In this surgical cohort, TIM-3 expression did not appear to be prognostic for survival. Conclusion: Our findings suggest that high TIM-3 expression occurs frequently in resected NSCLC, supporting the ongoing evaluation of anti-TIM-3 therapy in NSCLC. Additionally, TIM-3 expression was more frequently high in adenocarcinoma, normal lung, and a trend towards higher expression was noted in smokers. Future efforts will focus on identifying cell type specific TIM-3 expression via immunohistochemistry analysis and selecting patients for anti-TIM-3 clinical trials.

Keywords: Immunotherapy, TIM-3 (HAVCR2)

P2.01-079 THE SERUM LEVELS OF ALPHA-1 ANTITRYPSIN ARE STRONGLY ASSOCIATED WITH ITS LOCAL PRODUCTION BY TUMOR CELLS IN NSCLC PATIENTS

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Background: Lung cancer and chronic obstructive pulmonary disease (COPD) share a common etiology. Despite the known associations of alpha-1 antitrypsin (AAT) deficiency with COPD and COPD with lung cancer, few studies examined the association of AAT and lung cancer. We have investigated AAT serum levels in PiMM non-small cell lung cancer (NSCLC) patients with respect to PiMM controls with COPD and benign lung nodules since AAT is an acute-phase protein. The AAT tumor tissue expression was analyzed in NSCLC group to evaluate the potential contribution of cancer cells in AAT production. Methods: Serum and matched FFPE tissue samples were collected from 194 NSCLC patients (stages I-IV) with PiMM phenotype of AAT. The serum concentrations of AAT and CRP were measured by nephelometry. The AAT protein expression in NSCLC tumor cells was assessed by immunohistochemistry. Reference groups consisted of 183 PiMM COPD and 50 PiMM patients with benign lung nodules (hamartoma, tuberculosis, granuloma and other). Results: In NSCLC patients mean AAT serum concentration (195.5 mg/dl) was significantly higher than in COPD group (171 mg/dl) and patients with benign lung nodules (154 mg/dl) (p<0.0001). AAT concentration was significantly higher in SQC type (202 mg/dl) than ADC (175 mg/dl) (p<0.029) and in advanced (IIIb-IV, 247 mg/dl) versus early stage disease (I-II, 190 mg/dl) (p<0.0001). AAT levels significantly correlated with CRP (r=0.6, p<0.0001), however CRP level did not differentiate NSCLC from COPD. Importantly, the strong AAT expression observed in tumor tissue was positively associated with the higher AAT blood levels, while weak or no AAT expression directly correlated with the lower AAT blood levels (p=0.0079). Conclusion: We have demonstrated for the first time that the local production of AAT by tumor cells significantly contributes to the high levels of AAT in blood of NSCLC patients. The significant association of AAT serum levels with stage and histology of NSCLC may implicate clinical use of AAT as a biomarker or therapeutic target.

Keywords: concentration in serum, protein expression in tumour cells, alpha-1 antitrypsin (AAT), non-small cell lung cancer (NSCLC)

P2.01-080 MITOSIS COUNT OF LUNG ADENOCARCINOMAS: CORRELATION BETWEEN THE PHOSPHORYLATED HISTONE 3, NUMBER OF CANCER CELLS, NUCLEAR GRADE, AND PROGNOSIS

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Background: Nuclear grading can prognostically estimate inter-observer reproducibility in pulmonary adenocarcinoma (Nakazato Y. et al, Cancer, 2010 and JTO, 2013). However, no correlation has been shown between pathologic prognostic marker, number of cancer cells, and survival in pulmonary adenocarcinoma cases. Immunohistochemistry for phosphorylated histone 3 (pHH3), which is present during early prophase, is a reliable mitosis-specific marker. We evaluated the correlation between pH3-stained mitotic figures (PHMFs) and clinical outcome, comparing the results with those of PHMFs, Ki-67 labeling index, and number of cancer cells. Methods: Primary tumors were obtained from 104 patients with pulmonary adenocarcinomas (≤2 cm maximum dimension) who were treated surgically between January 2006 and December 2010 at Dokkyo Medical University Hospital. Specimens were stained with hematoxylin and eosin and pH3 and anti-Ki-67 antibodies. Cells were enumerated with a NanoZoomer Digital Pathology. Results were evaluated using receiver operating characteristic (ROC) curve analysis, the Kaplan–Meier method and Cox proportional hazards regression. Results: Cases judged negative by nuclear grading had significantly improved prognoses compared with positive cases (mean overall survival, 8.923 vs. 7.884 years; p=0.03). ROC curve analysis showed a cut-off of 0.740/10 hpf (area under the curve = 0.753; 95% CI = 0.594–0.891). Cancer cell index, defined as the number of cancer cells within 10 hpf, of ≤400 tended to be positive, and of ≤400 tended to be negative. PHMF/cancer cell index of ≥0.01 tended to be positive and of ≤0.01 tended to be negative. PHMF/cancer cell index (HR: 6.022, cancer cell index (HR: 6.399), and lymphatic invasion (HR: 5.308) were correlated with prognosis (p<0.02). The number of cancer cells was correlated with Noguchi’s classification and WHO pathologic type (See next page for figure).

Conclusion: PHMF/cancer cell index is useful for prognostic staging of pulmonary adenocarcinoma. PHMF/cancer cell index, cancer cell index, and lymphatic invasion are strongly correlated with prognosis. The number of cancer cells correlates with Noguchi’s classification and WHO pathologic type.

Keywords: Mitosis count, Phosphorylated histone 3, Nuclear Grading, pulmonary adenocarcinoma
Abstracts

POSTER SESSION 2 - P2.01: BIOLOGY/PATHOLOGY
MARKER FOR PROGNOSIS, PREDICTION - TUESDAY, DECEMBER 6, 2016

P2.01-081 CDC36 IS A NOVEL PROGNOSTIC CELL CYCLE PROTEIN AND TARGET FOR THERAPY IN NON-SMALL CELL LUNG CANCER
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Background: Lung cancer is the leading cause of cancer-related mortality worldwide with a 5 year survival rate of 15%. Non-small cell lung cancer (NSCLC) is the most commonly diagnosed form of lung cancer. Cisplatin-based regimens are currently the most effective chemotherapy for NSCLC, however, chemoresistance poses a major therapeutic problem. New and reliable strategies are required to avoid drug resistance in NSCLC. Cell division cycle associated 3 (CDC36) is a key regulator of the cell cycle. CDC36 modulates this process by enabling cell entry into mitosis through degradation of the mitosis-inhibitory factor WEE1. CDC36 itself is also degraded in G1 yet re-expressed in G2/M phase, to allow successful progression through the cell cycle. Herein, we describe CDC36 as a novel prognostic factor in NSCLC and target to delay or prevent cisplatin resistance in NSCLC. Methods: CDC36 expression was investigated in squamous and non-squamous NSCLC using several approaches including bioinformatic analysis of publicly available datasets, immunohistochemistry of a tissue microarray and western blot analysis of matched tumour and normal tissue and NSCLC cell lines. CDC36 function in NSCLC was determined using several in vitro assays by siRNA depleting CDC36 in a panel of three immortalized bronchial epithelial cell lines (HBEC) and seven NSCLC cell lines. Results: CDC36 transcripts and protein levels are elevated in NSCLC patient tissue and highly expressed in tumour cells relative to proximal normal cells. High mRNA levels are associated with poor survival in resected NSCLC. Depletion of CDC36 in vitro markedly impairs proliferation in seven NSCLC cell lines by inducing a mitotic cell cycle arrest, ultimately resulting in p21-dependent cellular senescence. Importantly, silencing of CDC36 also greatly sensitises NSCLC cell lines to cisplatin. In line with these in vitro data, NSCLC patients that have elevated levels of CDC36 and are treated with cisplatin have a poorer outcome than patients with reduced levels of the protein. To improve patient response to cisplatin, we are exploring novel strategies to suppress CDC36 expression in tumour cells. Conclusion: Our data highlight CDC36 as a novel factor in mediating NSCLC. We propose that evaluating novel strategies to target CDC36 may prove a useful strategy is enhancing the anti-tumour activity of platinum-based chemotherapy and may ultimately benefit patient outcomes by preventing cisplatin resistance.

Keywords: Cell cycle, non-small cell lung cancer, cisplatin chemotherapy, prognostic factor

POSTER SESSION 2 - P2.01: BIOLOGY/PATHOLOGY
MARKER FOR PROGNOSIS, PREDICTION - TUESDAY, DECEMBER 6, 2016

P2.01-082 TRANSCRIPTIONAL PROFILING IDENTIFIED THE ANTI-PROLIFERATIVE EFFECT OF MITOFUSIN-2 DEFICIENCY AND ITS RISK IN LUNG ADENOCARCINOMA
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Background: Mitofusin-2 (MFN2) was initially identified as a hyperplasia suppressor in hyper-proliferative vascular smooth muscle cells of hypertensive rat arteries, which has also been implicated in various cancers. There exists a controversy in whether it is an oncogene or exerting anti-proliferative effect on tumor cells. Our previous cell cycle analysis and MTT assay showed that cell proliferation was inhibited in MFN2 deficient A549 human lung adenocarcinoma cells, without investigating the changes in regulatory network or addressing the underlying mechanisms. Methods: We performed expression profiling in MFN2 knock-down A549 cells. Furthermore, we compared the expression profiling of a cohort consisting of 61 pairs of tumor-normal match samples from The Cancer Genome Atlas (TCGA). Results: The expression profiling in MFN2 knock-down cells suggested that cancer related pathways were among the most susceptible pathways to MFN2 deficiency. Next, we teased out the specific pathways to address the impact that MFN2 ablation had on A549 cells, as well as identified a few genes whose expression level associated with clinicopathologic parameters. In addition, transcriptional factor target enrichment analysis identified E2F as a potential transcription factor that was deregulated in response to MFN2 deficiency. (See figures next page)
Abstracts

POSTER SESSION 2 – P2.01: BIOLOGY/PATHOLOGY
MARKER FOR PROGNOSIS, PREDICTION –
TUESDAY, DECEMBER 6, 2016

P2.01-083 PROGNOSTIC FACTORS OF OVERALL SURVIVAL IN 150 RESECTED LUNG ADENOCARCINOMA PATIENTS
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Background: The 2011 IASLC/ATS/ERS pathological classification of pulmonary adenocarcinoma(ADC) gives new direction to clinical individualised treatment strategies and prognostic evaluation.We analyzed the prognostic effect of invasive ADC sub-types according to the new classification system. Methods: 150 invasive lung ADCs resected in West China Hospital from 2008 to 2013 was analyzed in 5% increments, and classified and graded according to their predominant patterns, as proposed by the IASLC/ATS/ERS. Clinical data,including smoking status, chemotherapy/radiotherapy after surgery and patient outcomes were collected. Overall survival was evaluated. Results: Tumor necrosis (p=0.033), poor differentiation (p=0.027), lymph node metastasis (p<0.001), surgical procedures (p=0.010), tumor diameter (p<0.001), and TNM stage (p<0.05 were significantly associated with overall survival (OS). Solid predominant ADCs (SPA) had a shorter OS than non-SPAs (43.5 vs 65.3 months, p=0.014). High-risk group (including SPA and micro-papillary predominant ADCs, MPA for short) had a poorer prognosis than low-risk group (including lepidic predominant, acinar predominant and papillary predominant ADCs, LPA,APA and PPA for short respectively) (44.4 vs 65.1 months, p=0.025). ADCs with papillary growth patterns (PP) had a better OS than those without PP (67.1 vs 42.5 months, p=0.001). In patients treated with chemo-or radiotherapy after surgery, OS of SPA and ADCs with PP were comparable to that of non-SPA and ADCs without PP, respectively (p value>0.05). Smoking also increased the risk of poor OS in certain subtypes significantly. Multivariate analysis showed SPA, high-risk group and ADCs with PP were independent prognostic factors for OS. Conclusion: Growth pattern and grading system are effective prognosticators of OS in invasive lung ADCs, which also influenced by other factors like post-operative chemo-/radio-therapy and smoking status. These results will give an instruction to the future individualized treatment of lung ADCs.

Keywords: pulmonary adenocarcinoma, histology, subtyping, Prognosis

POSTER SESSION 2 – P2.01: BIOLOGY/PATHOLOGY
MARKER FOR PROGNOSIS, PREDICTION –
TUESDAY, DECEMBER 6, 2016

P2.01-084 LINKER-PHOSPHORYLATED SMAD2 AND STAT3 INDUCE RESISTANCE TO TYROSINE KINASE INHIBITION IN LUNG CANCER
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Background: Cancer-associated inflammation develops resistance to the epidermal growth-factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) in non-small cell lung cancers (NSCLCs) harboring oncogenic EGFR mutations. The molecular mechanisms how the cytokines produced and activated in the tumor microenvironment such as transforming growth factor-β (TGF-β) and IL-6 regulate EGFR-TKI resistance remain largely unknown. Methods: To determine the mechanisms how Smad-mediated TGF-β signaling and STAT3-mediated IL-6 signaling regulate sensitivity and resistance to gefitinib, we treated HCC827 adenocarcinoma cell line harboring an oncogenic deletion within the EGFR (delE746-A750) with gefitinib, an activin receptor-like kinase5 (ALK5) inhibitor, EW-7197 and/or IL-6. Results: IL-6 and a TGF-β antagonist, EW-7197 synergized to suppress gefitinib-induced apoptosis of HCC827. Treatment with gefitinib induced interaction between unphosphorylated Smad2 and STAT3 in cytoplasm. IL-6 and/or EW-7197 significantly upregulated phosphorylation of Smad2 linker region. Linker-phosphorylated Smad2 at serine 245 and 255 residues interacted with phosphorylated STAT3 at tyrosine 705 and serine 727 residues to suppress gefitinib-induced apoptosis of HCC827. To determine the mechanisms how Smad-mediated TGF-β signaling and STAT3-mediated IL-6 signaling regulate sensitivity and resistance to gefitinib, we treated HCC827 adenocarcinoma cell line harboring an oncogenic deletion within the EGFR (delE746-A750) with gefitinib, an activin receptor-like kinase5 (ALK5) inhibitor, EW-7197 and/or IL-6. Results: IL-6 and a TGF-β antagonist, EW-7197 synergized to suppress gefitinib-induced apoptosis of HCC827. Treatment with gefitinib induced interaction between unphosphorylated Smad2 and STAT3 in cytoplasm. IL-6 and/or EW-7197 significantly upregulated phosphorylation of Smad2 linker region. Linker-phosphorylated Smad2 at serine 245 and 255 residues interacted with phosphorylated STAT3 at tyrine 705 and serine 727 residues to suppress gefitinib-induced apoptosis of HCC827. In contrast with Smad2, IL-6 and EW-7197 synergized to downregulate the expression of Smad3. Conclusion: Our data suggest that inhibition of phosphorylation of Smad2 linker region and STAT3 could prevent EGFR-TKI resistance in NSCLCs.

Keywords: Resistance, EGFR-TKI, Smad2, NSCLC

POSTER SESSION 2 – P2.01: BIOLOGY/PATHOLOGY
MARKER FOR PROGNOSIS, PREDICTION –
TUESDAY, DECEMBER 6, 2016

P2.01-085 EPIGENETIC PROFILE OF OLIGOPROGRESSIVE VERSUS WIDESPREAD NON-SMALL CELL LUNG CANCER PATIENTS
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Background: Genetic alterations associated with tumor progression and clinical outcome are different within patients. The different molecular mechanisms that drive various stages of non-small cell lung cancer (NSCLC) progression have not been fully elucidated. To address this issue, we determined the DNA methylation profile of oligoprogressive (OP) versus widespread (WP) disease in NSCLC patients. Methods: DNA from 14 NSCLC OP and 14 NSCLC WP patients were methylated and analyzed with an epigenome-wide DNA methylation array. Results: A total of 3,697 differentially methylated regions (DMRs) were identified, 1,752 hypomethylated and 1,945 hypermethylated in WP compared to OP. Among the 1,752 hypomethylated DMRs, 179 were significantly associated with poor overall survival. In 141 of these hypomethylated DMRs, the most hypermethylated region was found in the promoter regions of genes. Furthermore, we identified 228 hypomethylated DMRs overlapping with progression associated loci (PALs) and 43 hypermethylated DMRs overlapping with metastasis associated loci (MALs) in OP. Conclusion: Our results indicate that gene promoter hypomethylation may play a role in NSCLC progression and clinical outcome. Overall, our study highlights the importance of considering the different stages of NSCLC progression and the potential for epigenetic therapies in these patients.

Keywords: Epigenetics, Non-Small Cell Lung Cancer, Progression
P2.01-087 PROGNOSTIC SIGNIFICANCE OF CA IX OVEREXPRESSION IN STAGE III NSCLC PATIENTS RECEIVED NEoadJUVANT TREATMENT
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Background: The aim of study to investigate prognostic significance of carbonic anhydrase IX gene (CA IX) mRNA expression in stage III NSCLC patients received neoadjuvant treatment Methods: We have studied Carbonic Anhydrase IX (CA IX) mRNA expression at biopsy or surgical pathology tissues of 77 patient with Stage IIIA/B NSCLC received neoadjuvant treatment. CA IX mRNA expression were evaluated with 50 control. Total RNA were isolated from FFPE tissue from patients while the controls were isolated from the peripheral blood. Results: Median age is 56. Patients histology is 147 squamous cell carcinoma (SCC), 30 pts(39%) adenocarcinoma (AC). Neoadjuvant Chemotherapy (NeoAd) CT was given 45 pts (58.4%). Neoadjuvant chemotherapy( neoAd/CT/RT) was given 32pts (41.6%). Median Neoadjuvant chemotherapy cycles is 2-6. Radiotherapy median dose was 60 Gy(45-66). Surgery outcomes is Lobectomy 38pts (49.4%), sleeve lobectomy 1 pt (1.3%), Bilobectomy 6pts (7.8%) Left pneumonectomy(10.2%), right pneumonectomy 8pts (10.4%). Median disease free survival was 39 pts (50.6%). Two year disease free and overall survival was 59.6% and 71.4%. There was OS and DFS difference in favor of NeoAd CT 4-6 cycles versus 2-4 cycles (p=0.119 and p=0.034). There is no statistical difference (p=0.344) for CA IX mRNA expression between SCC and AC. There is no statistical difference for CA IX mRNA expression between NeoAd CT and NeoAd/CT/RT groups (p=0.199). There is no statistical difference for OS between median CA IX versus median groups (20 events/39 versus 20 events/38) Conclusion: There is no any prognostic significance of Carbonic Anhydrase IX expression on DFS and OS in Stage III A/B NSCLC patients received neoadjuvant treatments.
Keywords: neoadjuvant, stage III, Carbonic Anhydrase IX, NSCLC

P2.01-086 LUTEOLIN IS A NOVEL TARGET OF AXL RECEPTOR TYROSINE KINASE TO INHIBIT CELL PROLIFERATION AND CIRCUMVENT CHEMORESISTANCE IN LUNG CANCER CELLS
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Background: Axl receptor tyrosine kinase (RTK) plays a critical role in cell growth, proliferation, and anti-apoptosis. In this study, we demonstrated the effect of luteolin, a non-toxic flavonoid widely found in various plants, on expression and activation of Axl RTK in NSCLC, H460, and its cisplatin-resistant cell, H460/CisR. Methods: 1. Cell viability measurement & Clonogenic study. 2. Western blot analysis. 3. Promoter activity test. 4. Ectopic expression of Axl. 5. siRNA transfection for Axl knockdown. Results: Luteolin treatment of H460 and H460/CisR cells caused to decrease a dosedependent decline of Axl protein as well as mRNA levels. Axl promoter activity was also decreased by luteolin, suggesting the transcriptional down-regulation of Axl by luteolin. Axl phosphorylation upon its ligand, Gas6, was inhibited by luteolin, indicating that luteolin also abrogates Gas6-induced Axl phosphorylation. Next, it was found that treatment of both H460 and H460/CisR cells with luteolin decreased the cell viability and clonogenic ability in a dosedependent manner. We further observed the synergistic anti-proliferative effect of luteolin in cells transfected with Axl specific siRNA, while the reduction of its cytotoxic effect in Axl RTK overexpressing cells, confirming that luteolin exerts its anticancer potential via interference of Axl expression. In addition, luteolin was found to result in the increase of p21, a cyclin dependent kinase inhibitor, in H460 and H460/CisR cells. Conclusion: In summary, our data demonstrate that luteolin inhibits Axl expression and the activation which are associated with its anti-proliferative activity in both parental and clonosistant NSCLC cells. Thus, Axl seems to be a potent therapeutic target of luteolin to inhibit cell proliferation and to overcome chemoresistance of NSCLC cells.
Keywords: methylation, lung cancer, tumor suppressor gene
P2.01-099 PREDICTIVE VALUE OF AEG-1 EXPRESSION ON TUMOR RESPONSE BY LIQUID BIOPSY IN NSCLC PATIENTS TREATED WITH CHEMOTHERAPY

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Background: AEG1 is important in the aggressiveness of NSCLC and also contributes to induce chemoresistance in treatment of NSCLC. In this study, we will assess the predictive and prognostic values of AEG-1 expression on tumor response and survival according to mRNA concentration by liquid biopsy in NSCLC patients treated with chemotherapy. Methods: Patients were diagnosed with a advanced NSCLC (stage IIIb and IV). Patients were enrolled to be treated by chemotherapy as first-line treatment or for metastatic or recurrent disease with Eastern Cooperative Oncology Group (ECOG) performance status of 0–1. All patients underwent blood sampling before any cancer treatment and at first response evaluation. Response to chemotherapy was assessed using RECIST criteria. mRNA was extracted from plasma samples using the QIAamp Circulating Nucleic Acid Kit (Qiagen, Valencia, CA, USA) and quantification of mRNA was performed by real-time PCR (ABI 7900) with SYBR GREEN reagent expression assay for AEG-1. Results: A total of 12 patients (9 male and 3 female) with advanced NSCLC received platinum based doublets chemotherapy. Chemotherapy regimens included 8 cisplatin and 4 carboplatin with 5 pemetrexed, 4 paclitaxel, 2 gemcitabine and 1 vinorelbine. 7 of 12 (58.3%) were adenocarcinoma. The initial response rate of chemotherapy was 50% (6 of 12). After chemotherapy increased significantly compared with the expression before chemotherapy (Figure 1). After chemotherapy, the mRNA expression level of AEG-1 was not increased compared to the baseline expression (Figure 1).

Figure 1. mRNA expression of AEG-1 determined by liquid biopsy

Conclusions: This result suggests that mRNA concentration of AEG-1 from liquid biopsy could be a predictive biomarker of tumor response. Increased expression of AEG-1 contributed to the chemoresistance and caused lung cancer progression.

Keywords: lung cancer, chemoresistance, AEG-1
mechanisms of TAs+PO244 impact on tumor through immune cells we studied primary Lewis lung carcinoma (LLC) culture after the impact of macropathogen from LLC-bearing mice at the last stage of carcino genesis. Both TAs and PO244 were injected on 8th day after tumor cell inoculation. After the therapy macropathogen were contactless co-cultivated with primary LLC culture during 48 h. Mononuclear phagocyte fraction from peritoneal exudate of mice was obtained by standard Pietrangeli’s procedure. Apoptotic index and distribution of LLC cells in phases of cell cycle were assessed by flow cytometry. An adhesion potential was assessed with crystal violet. Results: Aforementioned combination revealed in 2-times increasing of LLC cells apoptotic level in comparison with primary LLC cells (without co-culture) and LLC cells under condition of co-cultivation with macropathogen from mice without therapy. TAs+PO244 therapy decreased population of LLC cells in proliferative pool (G2/M+ S phase) to 60%, whereas control rates were 65% and 60% in LLC cells without co-culture and LLC cells with macropathogen co-culture from mice without therapy, respectively. As the adhesion potential inversely correlates with cell ability to migrating, the in vitro data indicated that migration and tumor infiltration can be activate when tumor growing in vivo. We have shown in combined therapeutic scheme application of TA and PO244 on LLC. Monotherapy by TA stimulates tumor infiltration by lymphocytes insignificantly, whereas in combined therapy with PO244 this parameter is increased 2.4 times (p<0.05). Conclusion: Cytotoxic/cytostatic influence, which was expressed in increasing of apoptotic level and decreasing of cell population of proliferative pool was defined after co-cultivation of macropathogen from LLC-bearing mice treated by TAs+PO244 with primary LLC culture. This effect can be one of the possible mechanisms of TAs+PO244 impact on the lung cancer.

Keywords: lung cancer, Immunotherapy, Ligands of Toll-like receptors

POSTER SESSION 2 – P.2.01: BIOLOGY/PATHOLOGY
TARGETS FOR TREATMENT PREDICTION – TUESDAY, DECEMBER 6, 2016

P.2.01-092 PRMT5 IS A POOR PROGNOSTIC MARKER FOR NSCLC AND INHIBITION OF PRMT5 RESULTS IN INCREASED LUNG CANCER SENSITIVITY TO CISPLATIN AND RADIOTHERAPY

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Background: Protein arginine methyltransferase 5 (PRMT5), a member of the protein arginine methyltransferase family, has important regulatory function in many cellular processes through epigenetic control of target gene expression. Its overexpression is correlated either with the normal and its essential role in cell proliferation, transformation and cell cycle progression, PRMT5 has been recently proposed to function as an oncoprotein in cancer cells. In this study, we explore prognostic and predictive value of PRMT5 expression in lung cancer. Impact of PRMT5 inhibition in the setting of radiation therapy and platin-based chemotherapy was investigated.

Methods: PRMT5 expression levels in lung tumors as well as their paired normal tissue obtained from TCGA public databases were compared. The impact of PRMT5 expression on lung cancer patient survival was investigated by using “Director’s challenge Consortium for the Molecular Classification of Lung Adenocarcinoma” and JBR10 datasets. siRNA designed to target PRMT5 was used to transiently knockdown (KD) PRMT5 expression in several lung cancer cell lines. Clonogenic survival assays of lung cancer cell lines with increasing doses of cisplatin or radiation were performed in cells with normal endogenous PRMT5 expression or in cells after siRNA knockdown. Impact of PRMT5 knockdown on cell cycle, apoptosis, cell migration and invasion was investigated through cell cycle analysis, Annexin/PI flow cytometry, yH2A foci measurements in lung cancer cells with normal or reduced PRMT5 expression.

Results: PRMT5 expression is significant higher in lung tumors compared to paired normal tissue in TCGA datasets (LUAD and LUSC) with p value ≤0.0001. Patients with high PRMT5 expression presented lower overall survival at 5 and 3 years (p=0.02) from director’s challenge lung cancer study. Patients with low PRMT5 expression had significantly better DFS at 5 years (p=0.03) if they received cisplatin while patients with high PRMT5 expression did not benefit from cisplatin treatment (p=0.7). In several lung cancer cell lines, we observed 90% PRMT5 KD in transiently transfected cells at 48 h and 72 h post transfection as verified by western blot analysis. This inhibition of PRMT5 activity achieved by transient KD lead to a significant decrease in colony survival after radiation and cisplatin. There is an increase of cell population in G1 arrest in PRMT5 transient KD cells. Conclusion: High PRMT5 expression is associated with worse survival in lung cancer patients. Inhibition of PRMT5 in lung cancer cells results in sensitization to cisplatin and radiotherapy.

POSTER SESSION 2 – P.2.01: BIOLOGY/PATHOLOGY
MICROSEQUELAE – TUESDAY, DECEMBER 6, 2016

P.2.01-093 EXO-ALK PROOF OF CONCEPT: EXOSOMAL ANALYSIS OF ALK ALTERATIONS IN ADVANCED NSCLC PATIENTS

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Background: A subset of NSCLCs (approx. 5%), present alterations in ALK gene. This produces abnormal ALK proteins that induce cells to grow and spread. Different generation of ALK inhibitors are available for targeted therapy and their indication depends on the detection of ALK alterations in the tissue. Thus, it is mandatory to develop new techniques that allow us to demonstrate ALK alterations in peripheral blood. The purpose of this study is to analyze the feasibility to determine ALK alterations in exosomes (Exo-ALK) in NSCLC patients and determine the sensitivity and specificity of the technique. Methods: This study is performed in blind in a cohort 19 NSCLC with and without known alterations of ALK in tumoral tissue. ALK-positive tissue samples were identified by FISH or IHC and patients were included independently of stage and time of disease. Exosome RNA is isolated by exoRNeasy Serum/Plasma (Qiagen) and retrotranscribed by Transcript II First Strand CDNA Synthesis kit. The ALK gene present in the exosomes was determined by NGS and bioinformatic analysis from OncoDNA. Samples and data from patients included in the study were provided by the Biobank of the University of Navarra and were processed following standard operating procedures approved by the Ethical and Scientific Committees, were provided also by UZA Biobank and by the University of Naples Federico II. Results: The analyzed samples have been 16 ALK-EM4 tissue positive patients and 3 ALK-EM4 tissue negative, defined in this case by FISH. After analysis, we have been able to detect 9 positive ALK-EM4 patients, 8 negative samples, and 2 samples where the RNA was degraded. Looking at the clinical data, the 9 positive samples detected in the exosomal RNA were positive also for ALK-EM4 translocation in the tissue, and comparing the 8 negative samples, 3 were tissue negative and 5 tissue positive. These data show a specificity of 66% and a specificity of 100%. No correlation has been found comparing naive patients with treated patients. Conclusion: Exosomes are raising as one of the most promising tools to understand the tumor due to their stability in the blood and their similarity to the cells of origin. Our preliminary results show a high specificity and sensitivity of proof of concept of a new method to detect ALK alterations. Future studies with a bigger number of patients and a crossvalidation analysis are needed, but as we represent in this abstract, exosomes can represent an important tool for the clinical management of this specific NSCLC population.

Keywords: liquid biopsy, non small cell lung cancer, exosomes, ALK alterations

P.2.01-094 STROMAL ANTIGEN 1 (SA-1), A COHESIN, IS A NOVEL HOC REGULATOR FOR NSCLC

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Background: The molecular composition NSCLC is heterogeneous and clinically manifested as differential therapeutic responsiveness. It is increasingly appreciated that changes in high order chromatin (HOC) structure may play an important role in controlling gene expression and may be critical for the fundamental events in carcinogenesis. Here we present several HOC regulators are altered in lung cancer (e.g. Arid1a) from the cancer genome atlas work (TCGA), these occur in a minority of tumors suggesting involvement of other modulators. Recently, SA-1 (Stag-1), a member of the cohesin family, has been shown to be a HOC regulator in cancer via controlling chromatin looping and hence gene expression. Since no previous reports on cohesin in

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Abstracts

P2.02-001 ADVANCED LARGE CELL LUNG CANCER: BIOLOGICAL BEHAVIOR AND PROGNOSTIC FACTORS
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Background: Large cell lung cancer (LLLC) is a newly recognized clinicopathologic entity. The clinical criteria and optimal treatment for patients with LLC are not yet established. The aim of this study is to understand the clinicopathologic criteria of LLC. Methods: Among enrolled NSCLC cases attending National Cancer Institute – Cairo (NCI) between 2012-2014, we retrospectively reviewed those had LLC. Data regarding demographics, ECOG-performance status(PS), tumor histology, grade and stage, chemotherapy type, number of cycles, response to chemotherapy, overall and progression free survival(OS, PFS) were retrieved. Pearson’s(X²) test and Kaplan-Meier survival curves were used in statistical analysis. Results: Among 99 NSCLC cases, we identified squamous cell carcinoma (35.4%), adenocarcinoma(29.3%), undifferentiated(20.2%), large cell carcinoma (12.1%) and adenosquamous carcinoma(3%). Among 12 LLC cases; median age was 52 years (range;41-62 years), Male : Female was 3:1. Three-quarters of our cohort were PS=1. Progressive disease occurred in 58.3%. All were grade 3. Near 60% were stage IV while stage IIIB represents the remaining. Median OS was not reached while mean OS was 16.2 months. Median PFS was 6 months. Nearly 90% of disease progression were found within 1 year after start of chemotherapy. There was no difference in median OS or PFS in LLC vs other NSCLC(OS= not reached vs 13 months in other NSCLC(p=0.372) while PFS=6months in both groups(p= 0.915)). Further analysis by stage was conducted and revealed same results (in STAGE III; median OS was 12 vs 9 months (p=0.511), median PFS was 5months in both groups (p=0.956) See figure. Conclusion: Most cases of LLC represents high grade tumors and indeed aggressive treatment is warranted. Although previously reported data revealed poor prognosis of LLC (stage-I) in comparison to other NSCLC, our cohort represents similar prognosis in both groups in advanced stages

Keywords: Overall survival, progression free survival, large cell lung cancer, Advanced stage, National Cancer Institute

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P2.02-002 ASSOCIATION BETWEEN VEGF GENE FUNCTIONAL POLYMORPHISMS AND CLINICAL AND PATHOLOGICAL CHARACTERISTICS OF NON-SMALL CELL LUNG CANCER
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Background: Vascular endothelial growth factor (VEGF) is one of the most important angiogenic factor, which promotes endothelial cell growth and tumor neoangiascularization. VEGF expression is a marker of invasiveness and tumor progression in various cancers including in NSCLC. The aim of this study was to analyze association between VEGF gene functional polymorphisms and clinical and pathological characteristics of NSCLC. Methods: A total of 276 people with histological diagnosis of squamous cell carcinoma (SCC) and adenocarcinoma (AC) were included in this study. All patients gave their informed consent. VEGF gene polymorphisms were determined by PCR-RFLP analysis. Statistical analysis of the material was carried out using SNPstats online program. Results: Analysis of rs699947 polymorphism association with clinical and pathological characteristics of the tumor showed that patients with -2578GC genotype are more likely to have a greater extent of the primary tumor (T2-T4) as a small non-invasive cancer (T1): p = 0.005; OR = 2.54, 95% CI: 1.35-4.77. Association between this polymorphism and regional lymph node metastasis and the stage of the disease was found. A allele is protective against a more aggressive course of the disease: in patients with -2578AA genotype regional lymph node metastasis (N1-3) occur less frequently as compared to -2578CC genotype carriers (p = 0.0098; OR = 0.34, 95% CI: 0.17-0.69). -2578AA-allele carriers are less likely to have stages of the disease III and IV compared to -2578CC (p = 0.012 and 0.015 respectively). A trend of -2578GC polymorphism influence on the histological type of the tumor was identified. +936TT genotype is more common in patients with SCC as compared to AC (p = 0.055; OR = 4.78, 95% CI: 1.01-22.71). For rs2010963 polymorphism the association with clinical and pathological characteristics of NSCLC was not identified. Haplotype analysis of three studied polymorphisms of VEGF gene showed a significant association between -634C/-2578C+/936C haplotype and a small non-invasive cancer (p = 0.0068). -634G/-2578C/-936C haplotype carriers showed high aggressiveness of the disease (stage - p = 0.001; regional lymph node metastasis - p = 0.0014). Conclusion: -2578C allele of rs699947 polymorphism VEGF gene is associated with a large size of the primary tumor, the occurrence of regional lymph node metastasis and a greater stage of the disease. High aggressiveness of the disease was revealed in -634G/-2578C+/936C haplotype carriers. A significant association between -634C/-2578C/-936C haplotype and small non-invasive cancer was showed. Keywords: VEGF gene polymorphisms, vascular endothelial growth factor, non-small cell lung cancer, angiogenesis

P2.02-003 INCREASED CIRCULATING CYTOKERATIN-19 (CYFRA 21-1) IS PREDICTIVE OF POOR OUTCOME OF LOCALLY ADVANCED SQUAMOUS CELL CARCINOMA IN LUNG
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Background: Our goal was to evaluate the prognostic significance of circulating tumour markers in locally advanced squamous cell carcinoma of lung (LA-SCCL). Methods: Eligible patients included those with histologically proven LA-SCCL, available baseline tumour marker panel analysis (carcino-embryonic antigen [CEA], squamous cell carcinoma antigen 125 [SCC], cytokeratin-19 [CYFRA 21-1] and neuron-specific enolase [NSE]) and receiving definitive radiotherapy. Age, gender, radiation dose, baseline KPS, smoking history, weight, TNM stage, PET staging, RT technique and treatment modality (radiotherapy alone vs. sequential chemoradiotherapy or concurrent chemoradiotherapy) were also retrospectively collected. To dichotomise the continuous values of tumour markers into categorical variables, ROC analysis was adopted to identify the optimal cutoff values using the progression within 2 years after diagnosis as the endpoint. Cox regression based multivariate analyses were used to select independent factors correlated with various survival endpoints. Overall survival (OS), local regional progression free survival (LRPFS) and distant metastasis free survival (DMFS) were defined as the time from diagnosis until the first occurrence of specific event: death, local-regional recurrence or distant metastasis, respectively. Progression free survival (PFS) was defined as the duration between the cancer diagnosis and the date of any progression or cancer related death. Results: A total of 216 patients with LA-SCCL were analyzed. The optimal discriminative values for CEA, CA125, SCC, Cyfra 21-1 and NSE in predicting 2-y progression were 5.3 ng/ml, 17.0 ng/ml, 2.5 ng/ml, 5.2 ng/ml and 17.8 ng/ml respectively. Univariate analyses showed that increased Cyfra 21-1 was associated with inferior OS, LRPS, DMFS and PFS. Increased NSE was predictive of poor OS, DMFS and PFS. CEA also presented significant correlation with OS. Under multivariate analysis involving all clinical and tumour markers, IIIA stage, better performance status, CEA ≤ 5.3 ng/ml and Cyfra 21-1 ≤ 5.2 ng/ml were independently associated with improved OS. IMRT technique, RT dose ≥60 Gy and Cyfra 21-1 ≥ 5.2 ng/ml were correlated with better LRPS. None-smoker, IIIA stage, NSE ≤17.8 ng/ml were favourable predictors for DMFS. IIIA stage, KPS ≥80 and Cyfra 21-1 ≤5.2 ng/ml were advantageous factors related with favourable PFS. Conclusion: Baseline tumour marker panel including Cyfra 21-1, NSE and CEA can be prognostic of OS, local and distant tumor control for LA-SCCL, and should be recommended for baseline evaluation of tumour burden.

Keywords: Non-small cell lung cancer, squamous cell carcinoma, serum tumor marker, prognosis

P2.02-004 REAL-TIME MONITORING OF CIRCULATING TUMOR CELLS TO EVALUATE RESPONSE OF NEOADJUVANT CHEMOTHERAPY IN LOCALLY ADVANCED NSCLC
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Background: Enumeration and karyotyping of circulating tumor cells (CTCs) in therapeutic cancer patients is of particular clinical significance. The aim of this study is to evaluate therapeutic effect of neoadjuvant chemotherapy (NAC) by means of real-time monitoring of CTCs in locally advanced non-small cell lung cancer (NSCLC). Methods: Real-time monitoring of CTCs in the course of 2 cycles of platinum-based NAC was conducted in 34 locally advanced NSCLC patients. The integrated subtraction enrichment and immunostaining fluorescence in situ hybridization (SE-FISH) method was applied to detect and characterize CTCs in peripheral venous blood. Chest CT was used to evaluate therapeutic response with RECIST 1.1 as the evaluation criterion. Results: Of the 34 patients enrolled, 13 acquired partial response (PR) and 21 were stable diseases (SD) after NAC. The numbers of CTCs were found decrease in 70% of PR patients and only 25% of SD patients. The changes of CTC count were significantly different between PR and SD group (p<0.009). The positive rate of CTCs with triality of chromosome 8 increased after 2 cycles platinum-based NAC, and the elevation was even more remarkable in SD group. Conclusion: The changes of CTC count after NAC were in accordance with primary resistance to platinum-based chemotherapy. Real-time monitoring of CTC count and karyotype may be of clinical value in rapid evaluation of therapeutic effect and monitoring occurrence of chemo-resistance.

Keywords: non-small cell lung cancer, neoadjuvant chemotherapy, circulating tumor cell, Therapeutic response
clinical staging, amputation or radiotherapy are most often therapeutic options for pain palliation. We want to present an oligo-acrometastasis of fourth proximal phalanx of left hand from EGFR-mutant non-small cell lung cancer. Methods: A 58-year-old man was admitted with pain and swelling in fourth finger of his left hand (Figure 1A). Magnetic resonance imaging (MRI) of left upper extremity showed a destruction by a soft tissue measuring about 30x17 mm on the distal part of fourth proximal phalanx of left hand (Figure 1B-C). Three phase bone scan with technetium-99m methylene diphosphonate (MDP) revealed increased radiotracer uptake in the fourth finger. Diffuse increased uptake is seen at the left wrist secondary to the old fracture and trauma in both blood pool and metabolic phases and hypertrophic osteoarthropathy in both tibia (FigureE-F). Computed thorax tomography (CTT) revealed a 25x21 mm lobulated contour lesion in the posterior segment of right lower lobe (Figure 1H). CT-guided biopsy was performed and pathological examination showed non-small cell lung carcinoma—not otherwise specified (NSCLC-NOS). A 24x27x24 mm mass with SUV-max value 9.85 in the right lower lobe, right tracheobronchial and right hilar lymphadenopathies 13 mm in diameter was detected (SUV-max: 7.51) on PET-CT. Patient was staged as T1bN2M1b with oligoacrometastasis.

Results: His finger was amputated from metacarpophalangeal level and surgery margin was negative for tumour. Pathological diagnosis was metastatic NSCLC-NOS harbouring EGFR-L858R mutation. After curative treatment of acrometastasis, concurrent chemo-radiotherapy was planned for primary lung cancer as a therapeutic approach. He is still under treatment. Conclusion: Oligometastatic disease by acral involvement in NSCLC is extremely rare. Curative treatment approach should be consider for both primary tumour and metastasis side.

Keywords: Epidermal growth factor receptor mutations, Acrometastasis, non-small cell lung cancer, Oligometastasis

POSTER SESSION 2 – P2.02: LOCALLY ADVANCED NSCLC BIOLOGY – TUESDAY, DECEMBER 6, 2016

P2.02-006 TARGETED NEXT GENERATION SEQUENCING REVEALS PROGNOSTIC RECURRENT SOMATIC MUTATIONS IN THE GNAQ ONCOCENE IN NSCLC

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Background: GNAQ is a stimulatory αq subunit of heterotrimeric G-proteins that is highly mutated in human melanoma and currently has no targeted treatment. GNAQ protein is similar to the RAS protein, of which activating mutations occurring within the catalytic (GTPase) domain confer constitutive signaling activity of the RAS pathway. However, GNAQ mutations have not been documented in Non-Small Cell Lung Cancer (NSCLC). Therefore, the aim of this study was to examine genomic alterations in GNAQ and correlate its mutation status with clinical characteristics of NSCLC patients.

Methods: A cohort of 53 patients treated at the Thoracic Oncology Unit of the Instituto Nacional de Cancerología (INCan) of Mexico were screened in a mutation analysis of the GNAQ oncogene by targeted next generation sequencing (NGS). All information from the patients was recorded in a database containing clinicopathological characteristics. Results: Patients characteristics included a median age of 66 years (36-82 years), with 77% of females, 39% of smokers, 51% with wood smoke exposure and the predominant histology was adenocarcinoma (86%) with intermediate grade (acinar-papillary) in 65% of cases. In this study, recurrent somatic mutations in GNAQ were found in 37/53 patients (70%) with a mutant allele (GNAQmut) frequency over 1%. GNAQ mutations were more frequently found in adenocarcinoma and stage IV (p=0.054 and p=0.098 respectively). The GNAQmut allele was associated with metastasis to the Central Nervous System (CNS) and bones (p < 0.001). This mutation was associated with a decrease in overall survival (69 vs. 12 months, p = 0.047). Additionally, two of these GNAQ-mutated patients having co-occurring oncogenic mutations in GNAS and GNA11 exhibited faster disease progression and a poorer overall survival of only two months. There was no association between GNAQ and frequently mutated genes like EGFR, KRAS or MET. Conclusion: This is the first report of the presence of recurrent somatic mutations in GNAQ, GNA11 and GNAS oncogenes in NSCLC based on targeted NGS. We found a correlation between these genomic alterations and the patients response measured as disease progression and overall survival.

Keywords: GNAQ-Mutation, NSCLC, metastasis, Prognosis

POSTER SESSION 2 – P2.02: LOCALLY ADVANCED NSCLC CLINICAL OUTCOME – TUESDAY, DECEMBER 6, 2016

P2.02-007 TREATMENT OUTCOMES OF COMBINE CHEMORADIATION IN LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER: A SINGLE INSTITUTION STUDY

Pitchayaponne Klunklin, Imjai Chitapanarux

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Background: Since 1990s, the standard treatment for locally advanced non-small cell lung cancer (NSCLC) has been changed because the treatment by adding chemotherapy to thoracic radiation (TRT) was proved to gain a survival benefit over TRT alone. We conducted this study to report the outcome of combination treatment along with determine the factors that effecting survival. Methods: Medical records of 1,325 NSCLC patients who treated with radiotherapy in our division during 2008 to 2013 were reviewed. The patient characteristics, the management characteristics and outcome data were recorded. Univariate and multivariate analysis were performed to identify the prognostic factor for overall survival. Results: A total of 103 patients were included in the analysis. With a median follow up time 13.27 months, these patients had a median overall survival (OS) time of 21.4 months (95%-CI 17.6-25.2 months) and median progression-free survival (PFS) time of 11.67 months (95%-CI 9.69-13.65 months). The 2-year OS and PFS rate were 34.0 and 21.4%, respectively. For the patients treated by concurrent and sequential chemoradiation, the 2-year OS rate were 31.0% and 37.8% (p=0.349) and the 2-year PFS rate were 24% and 20.6% (p=0.690), respectively. The multivariate analysis revealed that age (hazard ratio (HR) 1.68, 95% CI: 1.06 – 1.69) and stage (HR 2.13, 95% CI: 1.43 – 3.39) were significant prognostic factors for overall survival. Conclusion: The treatment of locally advanced NSCLC in our hospital is feasible and the outcomes are comparable to others. The results of concurrent chemoradiation may improve further by careful patient selection.

Keywords: chemoradiation, Locally advance, non-small cell lung cancer

POSTER SESSION 2 – P2.02: LOCALLY ADVANCED NSCLC CLINICAL OUTCOME – TUESDAY, DECEMBER 6, 2016

P2.02-008 HOW DO WE REALLY TREAT PATIENTS WITH STAGE III NON-SMALL CELL LUNG CANCER (NSCLC)?

Allan Price, Sorcha Campbell, Sara Erridge, Janet Ironside, Felicity Little, Tamasin Evans, Melanie Mackean, Ailsa Patrizio

Edinburgh Cancer Centre, Western General Hospital, Edinburgh/United Kingdom

Background: About a quarter of patients with NSCLC have stage III disease. Standard treatment is cisplatin-based concurrent chemoradiotherapy, established in trials with participants younger and fitter than many patients seen in clinics. We have reviewed the treatment delivered to all patients registered on the South East Scotland Cancer Network (SCAN) database in 2011 to determine how many patients received standard of care therapy, and what might have influenced the decision not to administer this treatment. Methods: Individuals with stage III NSCLC presenting between January and December 2011 were identified from the SCAN database. Data were extracted on patient age, stage, histology, performance status, co-morbidities and treatment delivered. Results: 154 patients were identified who presented
P0.02-010 PROGNOSIS IMPACT OF OLIGOPROGRESSION FOLLOWING DEFINITIVE CHEMO-RT THERAPY IN STAGE III NON-SMALL CELL LUNG CANCER

Maria Saini1, Aj Rullan2, Milana Bergamo Sirven1, Arturo Navarro-Martin1, M Dolores Arnaiz1, Ramon Palmero1, Maria Plana1, Jose Carlos Ruffinelli2, Carles Mesia2, Susana Padrones2, Samantha Aso1, Isabel Brad1, Monica Arellano1, Joana Saldana1, Valentin Navarro2, Felipe Cardenal1, Ernest Nada1
1Department of Medical Oncology, Catalan Institute of Oncology, Hospital Clinic, Barcelona/Spain; 2Radiation Oncology Department, Catalan Institute of Oncology - Ircba Hospital, Hospitalet, Barcelona/Spain.

Background: The influence of recurrence pattern on outcome in stage III NSCLC following definitive chemoradiotherapy (CRT) has been scarcely addressed in the literature. Our aim was to analyze the relevance of oligoprogression (OP) in this clinical setting. Methods: Patients (pts) with stage III NSCLC who underwent concurrent CRT from 2010 to 2014 at the Catalan Institute of Oncology were retrospectively reviewed (n=170). Recurrence pattern at first progression was recorded. OP was defined as a single metastatic organ with up to 3 lesions. Overall Survival (OS) and Progression-Free Survival (PFS) were compared using Kaplan Meier method, and multivariate Cox proportional hazards model was developed. Results: Median age 64 (37-87); male 87%; ECOG=PS<1; 92%: histology: adenocarcinoma 34%, squamous 43%, NOS=large cell 36%;<121.5%, <m>02.5%, <m>03.1%, <m>03.9%. Platinum doublet: cisplatin 62%, carboplatin 38%. RT between 60-70 Gy (2Gy/fr): 94%. At median follow-up of 38 months (m), 108 of 170 pts relapsed (63%) and 66% died. mPFS was 13m (95% CI 10-16), mOS was 28m (95% CI 22-34). Twenty-five of pts who relapsed (23%) developed OP. Sites involved: visceral 17, brain 4, lymph nodes 3, bone 1. Treatments delivered: local therapy with curative intent 9; palliative intention 12; no treatment 4 (table 1). Among pts who relapsed, mOS was longer in those with OP (32m) as compared to pts without OP (18m, p=0.007). Pts with OP who received treatment, mOS according to curative or palliative intention was 53m versus 32m (p=0.1, respectively). In the multivariate Cox analysis of post-progression OS, OP remained a favourable prognostic factor (HR=0.36, 95% CI 0.17-0.74) independently of age, PS, stage, histology smoking history, and platinum doublet. Conclusion: OP was associated with substantial better prognosis in this cohort of pts treated with concurrent CRT. Local ablative therapies in the context of OP yielded promising results in terms of survival and warrants further investigation.

Keywords: NSCLC, stage III, recurrence pattern, oligoprogression.
management of patients with stage III NSCLC in Central European centres/ countries. The project is a multicentre, prospective, non-interventional registry. Methods: After ethical committee approval and signed informed consent, the clinical diagnostic and therapeutic procedures of consecutive patients diagnosed with stage III NSCLC (UICC7) were collected in web-based registry organised by the IBA MUNI, Brno, Czech Republic. Results: With cut-off 30 June 2016, 509 patients from 7 countries/16 centres were enrolled, median number of patients per centre being 23 (range 6-99). There were 16% males and 84% females who smoked. Performance status distribution was as follows: ECOG 0, 1, 2 and 3 in 29%, 56%, 12% and 3%, respectively. Squamous cancer was found in 52%, adenocarcinoma in 39%, and not otherwise specified in 5% and others in 4% of cases. Genetic mutations were examined in 119 (23%) patients, predominantly EGFR in 11% subjects with 16% positive findings, and the ALK mutation in 164 (48%) patients with no positive finding. Regular staging procedures were: X-ray (97%), chest CT (96%) and bronchoscopy (89%). Staging was completed by abdominal CT in 66% of patients, abdominal US in 29%, PET/CT in 22%, bone scan and ECOG MRI in 13%, respectively. Stage IIIA was found in 59% and stage IIIB in 41% of patients. NZ/NE nodes were diagnosed in 60% in 22% of patients. Pathological mediastinal lymph-node positivity was confirmed in 109 (21%) patients (8% EBUS, 0.2% VATS, 1% mediastinoscopy, 1% transbronchial biopsy and 13% surgery). Median time from diagnosis to first treatment was 23 days (range 0–22). Treatment procedures were surgery 138 (27%), chest radiotherapy 246 (48%) and chemotherapy 640 (89%) of subjects, respectively. Chemotherapy as only modality was given in 136 (27%) of patients. Surgery was combined with radiation in 6 cases, with chemotherapy in 79 (16%) cases and with both chemotherapy and radiotherapy in 37 (7%) patients. 25 (5%) patients underwent chemoradiotherapy including concurrent chemoradiotherapy in 67 (13%) cases. At the time of cut-off, 64% patients were alive, median survival time was not reached, and the 1-year estimated survival rate was 71%. Conclusion: The most prevalent histology was squamous cancer. Histopathological examination of mediastinal lymph nodes was positive in 52% of patients. Majority of patients (55%) were treated with combination therapy. Palliative chemotherapy only was given in 27% of patients. Survival data are not mature.

Keywords: treatment modality, non-small cell lung cancer, stage III, diagnostic procedures

P2.02-012 LONG-TERM SURVIVAL OF PHASE II OF FULL-DOSE ORAL VINORELBE COMBINED WITH CISPLATIN & RADIOTHERAPY IN LOCALLY ADVANCED NSCLC

Oscar Juan 1, Sergio Vazquez 2, Joaquin Casal Rubio 1, Jose Luis Frivida 3, Francisco Aparisi 4, José Muñoz 2, José García Sánchez 2, Regina Girónes 3, Martin Lazaro Quintela 2, Vicente Giner 2, Alfredo Sánchez Hernández 1

1. Medical Oncology, Hospital Universitari i Politécnic La Fe, Valencia/Spain; 2. Medical Oncology, Hospital Universitario Donostia, San Sebastián, Spain; 3. Medical Oncology, Hospital Universitario Dr. Negrín, Las Palmas de Gran Canaria, Spain; 4. Medical Oncology, Hospital Universitario Central de Asturias, Oviedo, Spain.

Background: Cisplatin (P) plus vinorelbine is one of the chemotherapy (CT) regimens associated with an adverse event specifically; subset of other medical costs. SD = standard deviation.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Overall Arm A Mean (SD)</th>
<th>Overall Arm B Mean (SD)</th>
<th>Concurrent Phase Mean (SD)</th>
<th>Concurrent Phase Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>551,319.90 ($334,169.11)</td>
<td>522,425.28 ($26,087.35)</td>
<td>28,856.03 ($25,745.12)</td>
<td>17,526.22 ($23,307.13)</td>
</tr>
<tr>
<td>Study treatment</td>
<td>31,203.67 ($51,217.62)</td>
<td>2,957.81 ($900.48)</td>
<td>15,719.30 ($3,447.07)</td>
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<td>Other medicala</td>
<td>20,110.22 ($28,856.03)</td>
<td>19,467.43 ($26,149.20)</td>
<td>13,367.73 ($25,725.51)</td>
<td>15,653.68 ($23,225.07)</td>
</tr>
<tr>
<td>Adverse- event-relateda</td>
<td>16,681.48 ($30,964.72)</td>
<td>16,061.84 ($24,356.95)</td>
<td>10,665.83 ($24,139.67)</td>
<td>13,193.85 ($21,860.89)</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>15,141.15 ($29,937.04)</td>
<td>13,562.54 ($23,156.58)</td>
<td>9,839.42 ($23,488.47)</td>
<td>11,778.76 ($20,017.99)</td>
</tr>
<tr>
<td>Concomitant medication</td>
<td>3,158.12 ($5,615.92)</td>
<td>4,238.32 ($5,421.06)</td>
<td>2,032.67 ($3,604.07)</td>
<td>2,498.43 ($3,997.82)</td>
</tr>
<tr>
<td>Monthly other-medical costs</td>
<td>4,529.33 ($5,594.09)</td>
<td>5,473.64 ($6,865.65)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P2.02-013 COSTING ANALYSIS OF PROCLAIM NON–SMALL CELL LUNG CANCER TRIAL DATA

Michele Wilson 1, Ryan Ziemietski 2, Belden San Antonio 3, Cheryl McAdie 4, Steven Thomas 5, Katherine Winfree 6

1. RIT Health Solutions, RIT Health Solutions, Research Triangle Park/NC/United States of America; 2. Eli Lilly and Company, Madrid/Spain; 3. RIT Health Solutions, Research Triangle Park/NC/United States of America; 4. Eli Lilly and Company, Indianapolis/IN/United States of America

Background: Standard care in inoperable stage III non-small-cell lung cancer (NSCLC) is concurrent chemoradiation. In the PROCLAIM trial, comparing concurrent pemetrexed-cisplatin (PemCis) and thoracic radiotherapy (RT) followed by consolidation vs pemetrexed versus etoposide-cisplatin (EtoCis) and RT followed by a consolidation platinum doublet in patients with locally advanced NSCLC, PemCis experienced significantly lower incidence of drug-related grade 3-4 adverse events (AE) and had similar resource use. Here, we estimate healthcare resource use costs associated within the PROCLAIM trial. Methods: Unit costs were applied to patient-level resource use (study drug, hospitalizations, radiotherapy, concomitant medications, laboratory tests, other procedures) to estimate total costs to a third-party US payer. Unit costs (in 2015 US dollars) were derived from publicly-available sources. Costs were compared using the nonparametric Wilcoxon rank sum test; sensitivity analyses were conducted. A subgroup analysis excluded patients with unusually long hospitalizations. Results: PemCis had significantly higher total costs than EtoCis (Table). While other medical costs were lower for PemCis in the concurrent phase, other medical costs were comparable for PemCis and EtoCis during the overall treatment mainly because PemCis patients survived in the trial longer (0.37 years) than EtoCis patients (0.22 years). Results were similar in the subgroup analysis.
study drug cost. However, other medical costs during the concurrent phase were lower for PemCis due to significantly lower hospitalization costs and lower concomitant medications use. When adjusting for overall treatment duration, other medical costs were favorable for PemCis. Pemetrexed patients may incur lower monthly other medical costs due to reduced hospitalization costs.

Keywords: pemetrexed, non-small cell lung cancer, locally advanced, economics

**POSTER SESSION 2 - P2.02: LOCALLY ADVANCED NSCLC**

**CLINICAL OUTCOME – TUESDAY, DECEMBER 6, 2016**

**P2.02-014 PERIOPERATIVE OUTCOMES AND DOWNSTAGING FOLLOWING NEOADJUVANT THERAPY FOR LUNG CANCER – ANALYSIS OF THE NATIONAL CANCER DATABASE**


1Thoracic and Cardiovascular Surgery, MD Anderson Cancer Center, Houston/ TX/United States of America, 2University of Texas, MD Anderson Cancer Center, Houston/TX/United States of America, 3Thoracic Head and Neck Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston/TX/United States of America

Background: Administration of chemotherapy prior to surgical resection is one of the strategies for the treatment of locally advanced non-small cell lung cancer (NSCLC). Potential benefits of this approach include improved treatment tolerance, tumor downstaging, and the evaluation of tumor response. Utilizing the National Cancer Database (NCDB), we sought to compare short-term perioperative outcomes and treatment response of neoadjuvant chemotherapy followed by surgery with surgery alone. Methods: We queried the NCDB Participant User File (PUF) for patients with clinical stage IIB-IIIA NSCLC who underwent definitive surgical resection for NSCLC between 2006-2013. We identified 83,274 patients with complete datasets who met the inclusion criteria. Patients were grouped by stage and perioperative outcomes were assessed, comparing those who underwent neoadjuvant therapy to surgery alone. Neoadjuvant therapy response was assessed by downstaging on final pathology in both unmatched and matched cohorts. Results: Neoadjuvant chemotherapy was administered to 11.9% (9,961/83,274) of potentially eligible patients. The incidence of neoadjuvant therapy increased with clinical stage; rates of 2.7% (995/37,453) for IIB, 5.4% (724/13,435) for IIA, 15% (2,048/13,619) for IIB, and 33% (6,194/18,767) for IIIA. All cause 30-, and 90-day mortality was 3.1% and 6.3% vs. 3.1% and 6.0% for neoadjuvant vs. surgery alone across all stages, (p<0.159, p<0.001). The unplanned 30-day re-admission rates were 3.8% vs. 4.3% for neoadjuvant vs. surgery alone (p<0.001). Median length of hospital stay was similar between the groups, 7.6 vs. 7.2 days for neoadjuvant vs. surgery alone (p<0.015); stage specific analysis revealed similar results. Overall downstaging was seen in 29.5% in the neoadjuvant group compared to 17% in the surgery group (p<0.001). Primary tumor downstaging occurred in 31.5% vs 9.5% (p<0.001) and nodal downstaging in 23% vs 14.4% (p<0.001) for neoadjuvant and surgery groups respectively. Additionally, significantly improved R0 resection rate was achieved for stages IIA and IIB in the neoadjuvant group 88.1% and 86.1% vs. 82.0% and 84.5% in the surgery group alone respectively (p<0.001 for IIA and IIB). Conclusion: In this largest review of perioperative outcomes and downstaging effect of neoadjuvant chemotherapy prior to definitive surgical resection for NSCLC, we demonstrate that the treatment strategy of neoadjuvant chemotherapy followed by surgery is safe and effective. Tumor downstaging and increased R0 resection rate in locally advanced lung cancer stages support the utilization of this treatment paradigm.

Keywords: neoadjuvant, induction therapy, Downstaging, Surgery

**P2.02-015 GUIDELINE CONCORDANT CARE IS ASSOCIATED WITH BETTER SURVIVAL FOR PATIENTS WITH STAGE III NON-CELL LUNG CANCER**


1Winship Cancer Institute, Emory University, Atlanta/ GA/United States of America, 2Mskcc, New York/NY/United States of America

Background: Current evidence-based guideline-concordant care (GCC) is administration of platinum-based chemotherapy during thoracic radiotherapy (TRT) for locally advanced non-small cell lung cancer (NSCLC) patients with good performance status. This study evaluates factors associated with lack of GCC. Methods: Patients (pts) with unrestaged stage IIIA/IIIB NSCLC diagnosed from 2005 – 2013 and Charlson-Deyo Score 0 were identified from the National Cancer Data Base (NCDB). Primary outcomes measured were receipt of GCC, defined by administration of chemotherapy with TRT commencing within 2 weeks of each other and minimum TRT dose of 60 Gy, and overall survival (OS). Multivariable logistic regression (MLR) modeling was performed to identify variables associated with non-GCC. Cox proportional hazard modeling was utilized to examine OS. Results: Patient characteristics (n=37,809) included: mean age 67.8 years; 55% male; 13% African American; 3.1% Hispanic, 6.0% ‘other’ race/ethnicity; 66% government-insured, mean tumor size 5.0 cm; 38% adenocarcinoma; 32% squamous cell carcinoma (SCC); 30% large cell/other histology. In total, 28% of pts received GCC. On MLR analysis, Hispanic pts were more likely to receive non-GCC (OR=1.34, p<0.001) compared to non-Hispanic pts. Uninsured pts were more likely to receive non-GCC (OR=1.57, p<0.001) compared to privately-insured pts. Patients treated in the western, southern, or northeastern U.S. were more likely to receive non-GCC (OR=1.43, 1.45, 1.21, all p values <0.001) compared to pts treated in the Midwest. Adenocarcinoma and large-cell/other histological types were more likely to receive non-GCC (OR=1.71, 1.39, both p<0.001) compared to SCC. For every one year increase in age or 50% increase in distance to treatment facility, patients had a 4% or 3% increased odds of not receiving GCC (OR=1.04, 1.03; p<0.001, p = 0.003, respectively). On hazard modeling, those receiving non-GCC had higher death rates compared to those receiving GCC (HR=1.56, p<0.001). Survival rates were lower for Hispanics receiving non-GCC versus GCC (HR=1.24, p<0.034). Other groups with lower OS for non-GCC versus GCC included: the uninsured (HR=1.61, p<0.001), treatment in the western, southern, or northeastern US (HRs=1.56, 1.40, 1.33, respectively, p<0.001), adenocarcinomas and large cell/other histologies (both HRs>1.0, p<0.001). Conclusion: Socioeconomic factors, including Hispanic ethnicity, lack of insurance, geographic location, and distance from treatment facility are associated with receipt of non-GCC. Patient and disease specific factors including increasing age and adenocarcinoma histology are also associated with non-GCC. Future interventions could target these groups to improve provision of GCC.

Keywords: evidence based, guideline concordant care, locally advanced non-small cell lung cancer (NSCLC), overall survival (OS), National Cancer Data Base (NCDB)

**POSTER SESSION 2 - P2.02: LOCALLY ADVANCED NSCLC**

**CLINICAL OUTCOME – TUESDAY, DECEMBER 6, 2016**

**P2.02-016 REAL WORLD EXPERIENCE WITH CHEMORADIOTherapy in locally advanced NSCLC**

Joaquin Gimeno, Irene Torres, Jorge Hernando, Ana Comín, Isabel Pajares, Mar Puertas, Pilar Felices, Ana Nuño, Juan Lao, Angel Artal Cortés

1Medical Oncology, Hospital Universitario Miguel Servet, Zaragoza/Spain, 2Radiation Oncology, Hospital Universitario Miguel Servet, Zaragoza/Spain

Background: Chemo-radiotherapy (CT-RT) remains the standard therapy for locally advanced Non-Small Cell Lung Cancer (LA-NSCLC). Concurrent therapy is the choice for fit patients, without a proven benefit of either induction or consolidation therapies. However, sometimes, as in our Health system, RT is not readily available from the beginning so CT is started upfront and RT started when possible. Methods: Charts from every patient treated with CT-RT in our Hospital between January/2008 and December/2015 for LA-NSCLC have been reviewed. Patient and therapy characteristics have been assessed. Results: 184 patients (p) were found: Median age 64 years (41-84), male 158/ (82,1%), PS 0/12/ 34, 2/8,6/1,6,1.6. Histology: adenocarcinoma 34%, squamous carcinoma 51,8%, NSG 2,7%, NSCLC with neuroendocrine features 10,9%. Stage IIA 32,1%, IIB 67,9%. CT included a platinum salt in 98.9% of cases: cisplatin in 57,6% and carboplatin in 41,3%. Most frequent companion drugs were vinorelbine (35.9% overall, 55.7% within patients treated with carboplatin) and paclitaxel (38.0%, 77.6% of those combined with carboplatin). Median number of CT courses was 4 (1-5), and median course when RT was started was third (1-4). Median survival was 22.5 months (18.2-36,7). It was longer in squamous carcinoma (23.1m), male patients (23.3m), stage IIA (27.5m) and cisplatin-treated (23.5m) although these differences were non-significant. The only significant factor for survival was PS (0=33.2 m, 1= 19.0m, p<0.001). No differences in patient characteristics existed with respect to stage, gender or histologic subtype between cis- or carboplatin-treated patients. More patients were treated with cisplatin (44/74 vs 77%) and carboplatin was preferred for PS1 patients (59/117= 50.4%, p<0.001). Conclusion: Despite our limitations to start RT early in the treatment of LA-NSCLC our results in real-world clinical practice were comparable to those reported in clinical trials. This was at the cost of increasing the burden of CT.
up to 4 courses. Probably, proper selection of patients was crucial, with PS 0 patients benefiting most from this approach. No major differences existed according the CT regimen administered (either the use of cis- or carboplatin as backbone or the partner drug used). In our experience, squamous carcinomas remained the most frequent subtype in LA NSCLC.

Keywords: NSCLC, Chemoradiotherapy

POSTER SESSION 2 – P2.02: LOCALLY ADVANCED NSCLC
CLINICAL OUTCOME – TUESDAY, DECEMBER 6, 2016

P2.02-017 A CLINICAL OUTCOME OF RESECTED SMALL-SIZED NON-SMALL-CELL LUNG CANCER 1 CM OR LESS IN DIAMETER WITH N2 LYMPH NODE METASTASIS
Yasafumi Katag1, Hideyuki Furumoto1, Shunsuke Shigefuku1, Junichi Maeda1, Koichi Yoshida1, Masaru Hagiwara2, Masatoshi Kakihina2, Naohiro Kawai2, Tatsuo Ohi2, Kinya Furukawa2, Norihiko Ikeda2
1Thoracic Surgery, Tokyo Medical University Ibaraki Medical Center, Ibaraki/Japan, 2Thoracic Surgery, Tokyo Medical University Hospital, Tokyo/Japan

Background: The detection of small-sized (< 1cm) non-small cell lung cancer (NSCLC) has increased with the development of high-resolution computed tomography. The reported 5-year survival rate of T1a (< 2cm) N0M0 patients is more than 80%, and that of p-T1a (<2cm) N2M0 patients has also steadily improved. Methods: Between 1991 and 2011, a total of 917 patients with small-sized (<2cm) NSCLC underwent curative pulmonary resection with systematic lymph node dissection at Tokyo Medical University Hospital and Tokyo Medical University/Ibaraki Medical Center. We retrospectively evaluated their postoperative clinical outcomes and survival rates. Survival was analyzed using the Kaplan-Meier method and log-rank test. Results: There were 46 (5.0%) patients with mediastinal lymph node metastasis in pT1a (<2cm). And there were 6 (0.6%) patients with pT1a (<2cm) N2M0. The histological types were 3 cases of adenocarcinoma, 2 cases of squamous cell carcinoma, and one large cell carcinoma. The respective status of lymph node metastasis was single station in 2 cases and multiple station in 4 cases. Skip lymph node metastasis was observed in 2 cases. There were 26 cases (56.3%) that were upstaged from clinical diagnosis in pT1a (< 2cm) N2M0 patients. There was one upstaging case from pT1a (<1cm) N1O to pT1a (<2cm) N2M0. The median overall survival period and 5-year survival of patients in pT1a (< 2cm) N2M0 was 52.1 months and 45%. And patients with pT1a (<1cm) N2M0 has 29.8 months and 0% (3 year overall survival rate was 33.3%). The recurrence rate was 71.7% (5/6) and disease free survival was 12.2 months. Conclusion: This study showed that 5.0% of small-sized (< 2cm) NSCLC had N2 disease and 0.6% of T1a (<1cm) NSCLC has N2. Moreover, 56.5% of small-sized (<2 cm) NSCLC was upstaged from clinical diagnosis to pathological diagnosis. The patients with pT1a (<1cm) N2M0 had worse survival data than the patients with pT1a (<2 cm) N2M0. We recommend systematic lymph node dissection for local treatment as well as accurate diagnosis. As multiple mediastinal node metastases showed an unfavorable prognosis, surgery combined with systematic treatment is recommended.

Keywords: Surgery, Small-sized NSCLC, pT1aN2M0, less than 1cm

POSTER SESSION 2 – P2.02: LOCALLY ADVANCED NSCLC
CLINICAL OUTCOME – TUESDAY, DECEMBER 6, 2016

P2.02-018 CHEMORADIOThERAPY IN ELDERLY PATIENTS WITH LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER
Ana Linhas1, Margarida Dias2, Sérgio Campainha2, Sara Conde2, Ana Barroso3
1Centro Hospitalar Vila Nova de Gaia/Esposito, Vila Nova de Gaia/Portugal

Background: The incidence of lung cancer increases with age and approximately 50% of non-small cell lung cancer (NSCLC) patients are over 70 years old. Combined modality therapy is standard of care for patients with unresectable locally advanced non-small cell lung cancer (NSCLC), however, despite the multitude of clinical trials performed, elderly patients have been under-represented in these studies. Objective: To investigate outcomes for elderly patients treated with chemoradiotherapy (CRT). Methods: Patients with locally advanced stage NSCLC admitted in a tertiary hospital, between 1th January 2014 and 31th may 2016, who received CRT were selected. Patients were divided in two groups by age (70 vs. >70 years old). Clinical-demographic variables, overall survival (OS) and progression free survival (PFS) were compared between the two groups. Results: Fifty-one patients were included. The results are presented in the table:

<table>
<thead>
<tr>
<th>Gender</th>
<th>n=23(45.1%)</th>
<th>n=28(54.9%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>19(82.6)</td>
<td>26(92.9)</td>
<td>0.390</td>
</tr>
<tr>
<td>Performance status (at diagnosis)</td>
<td></td>
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<tr>
<td>0</td>
<td>6(26.1)</td>
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<td>0.172</td>
</tr>
<tr>
<td>1</td>
<td>16(69.6)</td>
<td>13(46.4)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1(4.3)</td>
<td>5(17.9)</td>
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<tr>
<td>Weight loss (at diagnosis)</td>
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<tr>
<td>0%</td>
<td>14(60.9)</td>
<td>16(57.1)</td>
<td>0.895</td>
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<tr>
<td>5%</td>
<td>6(26.1)</td>
<td>7(25.0)</td>
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</tr>
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<td>10%</td>
<td>3(13.0)</td>
<td>5(17.9)</td>
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<td>Clinical stage</td>
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<tr>
<td>IIIA</td>
<td>10(43.5)</td>
<td>17(60.7)</td>
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<tr>
<td>IIIB</td>
<td>13(56.5)</td>
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<td>Comorbidities</td>
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<tr>
<td>Heart failure</td>
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<td>4(14.8)</td>
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<tr>
<td>Hypertension</td>
<td>7(30.4)</td>
<td>20(74.1)</td>
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<tr>
<td>Dyslipidemia</td>
<td>5(21.7)</td>
<td>12(44.4)</td>
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<td>Chemotherapy regimen</td>
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<tr>
<td>Carboplatin</td>
<td>5(21.7)</td>
<td>20(71.4)</td>
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<tr>
<td>Cisplatin</td>
<td>18(78.3)</td>
<td>8(28.6)</td>
<td></td>
</tr>
<tr>
<td>CRT[n;(%)]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sequential</td>
<td>6(26.1)</td>
<td>11(39.3)</td>
<td>0.320</td>
</tr>
<tr>
<td>Concurrent</td>
<td>17(73.9)</td>
<td>17(60.7)</td>
<td></td>
</tr>
<tr>
<td>Second line treatment[n;(%)]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>16(69.6)</td>
<td>21(75.0)</td>
<td>0.320</td>
</tr>
<tr>
<td>Yes</td>
<td>7(30.4)</td>
<td>7(25.0)</td>
<td></td>
</tr>
</tbody>
</table>

Comparing with younger group the elderly group presented significant worse OS and longer PFS, although without statistical significance [respectively, median 7 vs. 12months (p=0.006) and median 11.5 vs. 8months (p=0.687)]. Elderly patients with higher PS presented worse survival (p=0.045). Patients submitted to a chemotherapy regimen with cisplatin presented better OS and PFS in both groups, although only statistical significant for the OS in patients under 70 years (p=0.023). There was no influence of other variables on OS and PFS. Conclusion: In our sample we was an age important prognostic factor in patients submitted to CRT but other factors, as PS, also can influence prognosis. In both groups patients treated with cisplatin presented superior OS but less patients above 70 years received this treatment. Elderly patients could be considered for CRT treatment but each case should be analysed individually. More studies are needed to guide treatment in this population.

Keywords: elderly, survival, Locally advanced NSCLC, Chemoradiotherapy

POSTER SESSION 2 – P2.02: LOCALLY ADVANCED NSCLC
CLINICAL OUTCOME – TUESDAY, DECEMBER 6, 2016

P2.02-019 LUNG CANCER IN YOUNG ADULTS (AGE GROUP 18-50 YRS): PRESENTATION, CLINICAL FEATURES AND TREATMENT
Balaji Varadhan1, Neena Kalsi1, Samreen Ahmed1, Kimilu Ryanna1
1Oncology, Leicester Royal Infirmary, Le Ww/United Kingdom, 2University Hospital of Leicester, Nottingham/United Kingdom, 3University Hospitals of Leicester, Leicester/United Kingdom

Background: Non small cell lung cancer in young adults appears to be increasing over recent years. It’s a devastating illness both for the patient and their family. It has got significant socioeconomic implications. Methods: Data were analysed for the period between 2010-2015 from the University Hospitals of Leicester data base. Young adults were defined as age less than 70-years old. Clinical-demographic variables, overall survival (OS) and progression free survival (PFS) were compared between the two groups. Results: From a total of 93 patient’s we found the majority had adenocarcinoma, with 56% in the 18-39 age group and 63.6% in 40-50 age group. A greater proportion
of patients in each age group were found to have a performance status of 0. The number of male patients were noted to be slightly higher between 18-39 (55%), compared to the 60-80 age groups, where there was a female predominance (57%). The majority of patients in both age groups were found to have a good performance status and a larger proportion of patient's eGFR status was negative. Young adults were more likely to have surgery and chemotherapy due to their better performance status. Conclusion: In our cohort of young adults with lung cancer, the majority of patients had a good performance status despite late stage disease. They were likely to be fit for treatment and have longer survival outcomes.

**POSTER SESSION 2 - P2.02: LOCALLY ADVANCED NSCLC**

**P2.02-020 PATTERN OF CARE OF INOPERABLE LOCALLY ADVANCED (LA) NSCLC IN ELDERLY PATIENTS: ANALYSIS OF THE EXPERIENCE OF TWO ACADEMIC ITALIAN HOSPITALS**

Marco Perna, Vieri Scotti, Alessio Brunelli, Gabriele Simontacchi, Vanessa Di Cataldo, Emmanuela Olmetto, Giulio Alberto Carta, Roberta Grassi, Carlotta Becherini, Carla Di Luca Cardillo, Benedetta Agresti, Camilla Comin, Katia Ferrari, Elisa D’Angelo, Polina Vasilyeva, Bruno Meduri, Frank Lohr, Luca Voltofini, Lorenzo Livi

Oncology, Radiation Oncology Unit, Florence/Italy; 2Radiotherapy Unit, AOU Policlinico of Modena, Modena/Italy; 3Cyberknife Center - I.P.C.A (Istituto Fiorentino Di Cura Ed Assistenza), University of Florence, Florence/Italy; 4Department of Experimental and Clinical Medicine, University of Florence, Section of Surgery, Histopathology and Molecular Pathology, Florence/Italy; 5Cardiothoracic Department, Pneumology and Thoracic Pneumopathology Unit, Azienda Ospedaliero-Universitaria Careggi, Florence/Italy; 6Thoracic Surgery Unit, Florence/Italy

Background: Optimal treatment in LA NSCLC patients is still debated. In fit patients concomitant radio-chemotherapy (RCT) seems to be the best treatment in terms of local control (LC), progression free survival (PFS) and overall survival (OS) while sequential RCT is a good alternative in unfit patients. Moderately hypofractionated radiotherapy improve OS in recent studies. Elderly patients often cannot be offered multimodality treatments. We report our experience with over 70 years old LA NSCLC patients deemed unfit for surgery. Methods: In fit patients concomitant radio-chemotherapy (RCT) seems to be the best treatment in terms of local control (LC), progression free survival (PFS) and overall survival (OS) while sequential RCT is a good alternative in unfit patients. Moderately hypofractionated radiotherapy improve OS in recent studies. Elderly patients often cannot be offered multimodality treatments. We report our experience with over 70 years old LA NSCLC patients deemed unfit for surgery. Methods:

**Patients’ Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Median 75</td>
</tr>
<tr>
<td>Range</td>
<td>70-83</td>
</tr>
<tr>
<td>Gender</td>
<td>Male 50 (70%); Female 21 (30%)</td>
</tr>
<tr>
<td>Performance Status</td>
<td>0 36 (51%); 2 6 (8%)</td>
</tr>
<tr>
<td>Histology</td>
<td>Adenocarcinoma 31 (44%); Squamous Cell Carcinoma 39 (55%); Large Cell Carcinoma 1 (3%)</td>
</tr>
<tr>
<td>Stage</td>
<td>Ila/Ilb 12 (17%); Ilb 9 (15%); Ilb 20 (28%)</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>Concomitant 9 (13%); Sequential 62 (87%)</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>Cycles: median 4; Cycles: range 1-8</td>
</tr>
<tr>
<td></td>
<td>Median Dose 62,3 Gy; Moderate hypofractionation 26 (37%); Conventional fractionation 45 (63%)</td>
</tr>
</tbody>
</table>

**Table 1**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD N(%)</td>
<td>concurrent N=737; sequential N=101</td>
</tr>
<tr>
<td></td>
<td>461 (62.6); 68 (68.3)</td>
</tr>
<tr>
<td>ePDfirst N(%)</td>
<td>-patients with concomitant cerebral metastases</td>
</tr>
<tr>
<td></td>
<td>401 (87.0) - 38 (9.5)</td>
</tr>
<tr>
<td></td>
<td>62 (89.9) - 8 (12.9)</td>
</tr>
<tr>
<td>median time to ePD (5%) months</td>
<td>17.5 [15.0-20.0]; 14.3 [11.9-16.7]</td>
</tr>
<tr>
<td></td>
<td>0.16</td>
</tr>
<tr>
<td>PD N(%)</td>
<td>LDC N=391; cyclic dose N=346</td>
</tr>
<tr>
<td></td>
<td>245 (62.7); 216 (62.4)</td>
</tr>
<tr>
<td></td>
<td>0.33</td>
</tr>
</tbody>
</table>

Characteristics of patients and treatments are summarized in table 1. All patients were treated with a platinum based doublet of chemotherapy (CT). RT target volumes included the primary lung tumor and involved mediastinal lymphnodes as defined on pre-treatment contrast enhanced CT scan. Elective nodal irradiation was not performed. Acute/late toxicities were reported in accordance to 4.0 CTCAE scale. Clinical response was evaluated according to RECIST criteria. Results: At a median follow up of 10 months clinical response was evaluable in 69/71 patients obtaining a partial response in 35 of them, stable disease in 17, progressive disease in 17 patients. Twenty six patients experienced a local relapse within RT primary tumor volume, while 13 on nodal volume (5 patients both tumor and nodal relapse). 22 patients developed metastatic disease. One and two year OS was 62.3% (SE±6.2%) and 24.5% (SE±7.8%) respectively, while 1- and 3-year PFS was 65.1% (SE±6.9%) and 9.7% (SE±5.7%) respectively. At univariate analysis, tumor dimension (p=0.002) was the only prognostic factor statistically significant for OS. G1-G2 acute toxicity was observed in 45 patients: 36/62 in sequential CRT (3.63 described also chronic toxicity). Survival and local control (LC) were found to be excellent (LC=91% at 1 year). Conclusion: RCT is feasible in elderly patients; multidisciplinary evaluation is needed in order to reserve CRT to very fit patients.

Keywords: concomitant radio-chemotherapy, sequential radio-chemotherapy, elderly, Locally Advanced NSCLC
Conclusion: Sixty-three percent of stage III NSCLC patients developed PD, of whom 87% had EOPD. Incidence of EOPD is independent of the specific chemotherapy regimen.

Keywords: Locally advanced NSCLC, chemoradiation, extracranial progression

POSTER SESSION 2 – P2.02: LOCALLY ADVANCED NSCLC
CLINICAL OUTCOME – TUESDAY, DECEMBER 6, 2016

P2.02-022 FOR DOWN STAGED CLINICAL N3 M0 NON-CELL LUNG CANCER PATIENTS CHEMO-RADIOThERAPY FOLLOWED BY SURGERY CAN IMPROVE SURVIVAL
Jitian Zhang1, Toshikiko Sato2, Makoto Sonobe1, Toyofumi Chen-Yoshikawa1, Akhiro Aoyama1, Yoshi Menju1, Kyoko Hijiy1, Hideki Motoyama1, Yukinori Matsuo1, Young Kim1, Hiroshi Date2
1University of Hong Kong Shenzhen Hospital, Shenzhen/China, 2Thoracic Surgery, Graduate School of Medicine, Kyoto University, Kyoto/Japan, 3Radiology, Graduate School of Medicine, Kyoto University, Kyoto/Japan, 4Respiratory Medicine, Graduate School of Medicine, Kyoto University, Kyoto/Japan

Background: Non-small cell lung cancer (NSCLC) patients with clinical (c)-N3 M0 are conventionally regarded as inoperable. However, the role of surgery for such patients clinically down staged after chemo-radiotherapy has not been ascertained. We retrospectively compared the outcome after chemo-radiotherapy plus surgery for down staged patients versus only conventional chemo-radiotherapy. Methods: Patients treated at our institute from 2000 to 2016 for primary NSCLC with c-N3M0 were identified. Amongst them, six patients received lung resection surgery after chemo-radiotherapy was given and clinical evidence of downstaging found. Fifty patients received only conventional chemo-radiotherapy during the same period. Survival was estimated using the Kaplan-Meier method. Results: All of the 6 patients receiving chemo-radiotherapy plus surgery, are recurrence-free survival. The survival time ranged from 5 to 91 months. The 5-year overall survival for the patients receiving surgery was 100% compared with 24% for the 50 patients who did not receive surgery (p=0.04). Conclusion: Our results suggest that the combination of chemo-radiotherapy plus surgery may improve survival for preoperatively down staged c-N3M0 NSCLC patients. These results should be validated by large-scale, prospective, randomized trials.

Keywords: NSCLC, Surgery, down staged, clinical N3

POSTER SESSION 2 – P2.02: LOCALLY ADVANCED NSCLC
CLINICAL OUTCOME – TUESDAY, DECEMBER 6, 2016

P2.02-023 NEoadjuvANT CHEMOTHERAPY AND CONCURRENT FULL-DOSE RADIATION THERAPY FOLLOWED BY SURGERY FOR STAGE IIB NON-CELL LUNG CANCER CARCINOMA OF THE LUNG
Sherry Yan1, Seth Crockford1, Anshu Jain1, Christina Wu1, Frank D’Ovidio1, Lyall Gorenstein1, Matthew Bacchetta1, Mark Ginsburg1, Balazs Halms1, Mark Stoos1, Joshua Sonett, Simon Cheng
1Columbia University Medical Center, New York/New York/United States of America, 2Mount Sinai St. Luke’s-Roosevelt Hospital, New York/New York/United States of America, 3Yale University Medical Center, New Haven/New Haven/United States of America, 4University of California Los Angeles, Los Angeles/New York/United States of America, 5Department of Hematology/Oncology, Albert Einstein/Englewood Cancer Center, Bronx/New York/United States of America

Background: The role of neoadjuvant chemoradiation and surgery in patients with stage IIB non-small cell lung cancer (NSCLC) is unclear. Previous studies have suggested that select patients may benefit from this multimodality approach. We retrospectively reviewed patients with stage IIB NSCLC treated by trimodality intent with induction chemotherapy and concurrent full-dose radiation therapy followed by either surgery at our institution. Here we report survival and toxicity data in our cohort. Methods: Eight patients treated from 1999 to 2011 with neoadjuvant chemoradiotherapy for stage IIB NSCLC were included in the retrospective review. Five (63%) had pathologically proven N3 disease; 1 (13%) had radiographic evidence of N3 disease (2cm adenopathy with SUV>6); 2 (25%) had T4 disease due to involvement of multiple ipsilateral lobes. All 6 patients with N3 disease had minimal radiographically enlarged N3 nodes (fewer than 3) before treatment. Induction chemotherapy consisted of carboplatin or cisplatin doublet. Concurrent RT prescription consisted of 45Gy in 25 fractions to the mediastinum and primary tumor; most patients received a boost to at least 60Gy to gross disease. After re-evaluation, patients received surgery within three months of completion of induction therapy. Inoperable patients received consolidative chemotherapy. Results: Six patients (86%) received at least 59.4Gy to the primary tumor. Six patients underwent resection. 2 had pneumonectomy and 6 had lobectomy. A complete (R0) resection was achieved in all patients. Mediastinal nodal clearance (N2/3 negative) was seen in five (83%) patients. A complete pathological response was seen in three (50%) patients. With a median follow up of 45 months for all patients, the median overall survival (OS) was 52.8 months. The median progression-free survival (PFS) was 48.4 months. Median OS was 52.8 months for patients who achieved MNC, 5.7 months in one patient with residual mediastinal nodal disease (P=0.025), and 0.9 months in those who did not receive surgery. There was grade 3 postoperative pulmonary complications and no treatment-related mortality within the follow up interval. Conclusion: Data from our small cohort provide important preliminary evidence that neoadjuvant chemotherapy with concurrent full-dose radiation therapy followed by surgery may be a feasible treatment option for select patients with stage IIB NSCLC. Toxicity is acceptable, and survival outcome compares favorably with that of patients with IIIA NSCLC treated with trimodality therapy.

Keywords: Stage IIB Non-Small Cell Lung Cancer, trimodality therapy

POSTER SESSION 2 – P2.02: LOCALLY ADVANCED NSCLC
CLINICAL OUTCOME – TUESDAY, DECEMBER 6, 2016

P2.02-024 PHASE I AND II TRIAL OF INTRAPLEURAL PACLITAXEL INJECTION FOR NON-SMALL-CELL LUNG CANCER PATIENTS WITH MALIGNANT PLEURAL EFFUSIONS
Masato Saeki1, Akiyoshi Okada2, Kayo Sakon2, Masaki Anzai3, Miwa Morikawa2, Yukishiro Umeda2, Shingo Ameshima2, Tamotsu Ishizuka2, Takaaki Koshiji3
1Department of Surgery (II), University of Fukui, Fukui/Japan, 2Department of Surgery (II), University of Fukui, Fukui/Japan, 3Department of Internal Medicine (III), University of Fukui, Fukui/Japan

Background: The presence of malignant pleural effusion (MPE) frequently indicates locally advanced non-small cell lung cancer (NSCLC). The conventional management of MPE involves pleurodesis using a sclerosant substance. The Peng et al. reported injection into chest cavity using paclitaxel for 18 MPE cases. In this report overall response rate was 92.9%. No disease progression was noted among evaluable patients. Therefore we focused on Paclitaxel which had antitumor effect and a pleural effusion control, and planned clinical trials phase I and II for the treatment of MPE. Methods: The primary objective of this study was to evaluate the efficacy of paclitaxel pleurodesis, the side effects and systemic antitumor effect. Patients were enrolled cytologically proven malignant pleural effusion of NSCLC. Radiotherapy and systemic chemotherapy were also not allowed within 4 weeks. After adequate drainage and assurance of lung re-expansion, paclitaxel diluted in normal saline was infused through a double lumen catheter. The starting dose was 100 mg/m2 with dose escalation schedule of 125, 150, and 175mg/m2. The catheter was clamped for 24 hrs. Chest drainage was continued until daily drainage was under 200 ml, and the tube was removed. To measure paclitaxel concentration, serum and pleural fluid samples were collected 0.5, 1, 3, 6, 24, 72hrs after the end of drug instillation. The treatment response of malignant effusion was evaluated according to the following criteria: complete response (CR), no fluid reaccumulation for at least 4 weeks as determined by CT scan; partial response (PR), recurrence of effusion to less than 50% of the original effusion volume within 4 weeks after treatment; failure, recurrence of effusion greater than 50% of the original volume, patients were symptomatic and need for thoracentesis to relieve symptoms within 4 weeks. The criteria for main tumour lesion response; failure, recurrence of effusion greater than 50% of the original effusion volume within 4 weeks after treatment; failure, recurrence of effusion greater than 50% of the original volume, patients were symptomatic and need for thoracentesis to relieve symptoms within 4 weeks. The criteria for main tumour lesion response. Results: From April 2009 to November 2012, 12 patients were enrolled. There were minimal local and systemic toxicities. The serum level of PXL of the cases without the effect of treatment was significantly higher than the cases with the effect of treatment without the effect. Over all response rate was 67%. No disease progression was noted among evaluable patients. Conclusion: We decided to plan a late phase II study of the therapy with 175 mg/m2, because it was not dosage-dependent even if it was a low dose and serum level-dependent.

Keywords: intrapleural injection, malignant pleural effusion, paclitaxel
P2.02-025 CONTINUOUS INTRAVENOUS PUMPING ENDOSTAR COMBINED WITH RADIONECHEMOTHERAPY IN UNRESECTABLE STAGE III NON-SMALL-CELL LUNG CANCER
Hong Lian Ma, Zhou Guang Hui, Lu Jun Zhao, Yu Jin Xu, Yi Rui Zhai, Run Ye Wu, Qing Song Pang, Guang Yin Zhu, Dong Ming Li, Yu Tang, Jun Liang, Yup Kong, Ming Chen, Lv Hua Wang
1Department of Radiation Oncology, Zhejiang Cancer Hospital, Zhejiang Key Laboratory of Radiation Oncology, Hangzhou, China; 2Cancer Hospital, Chinese Academy of Medical Science, Peking Union Medical College, Beijing, China; 3Tianjin Medical University Cancer Hospital, Tianjin, China; 4Peking University School of Oncology, Beijing Cancer Hospital, Beijing, China.

Background: Preclinical models have shown that recombinant human endostatin (Endostar) can transiently normalize the tumor vasculature to make it more efficient for oxygen delivery, which provides a treatment window of enhancing tumor radiosensitivity. This study is to evaluate the safety and efficacy of continuous intravenous pumping (CIP) of Endostar combined with standard concurrent radiochemotherapy for unresectable stage III non-small-cell lung cancer (NSCLC). Methods: In this prospective study, patients with unresectable stage III, or II, NSCLC received CIP of Endostar (7.5mg/m² on day 5) in 5 days at week 1, 3, 5, and 7. During week 2-8, patients received two 28-day cycles of etoposide 50mg/m² on day 1-5 and cisplatin 50mg/m² on day 1, 8, with concurrent thoracic radiation of 60-66 Gy in 30-33 fractions over 6-7 weeks. Acute toxicities were evaluated using CTCAE 3.0. Tumor response was evaluated using RECIST 1.1 criteria. Results: Between Nov. 2012 and May, 2016, 67 patients were eligible for toxicity and efficacy evaluation, including 56(83.6%) male and 11(16.4%) female, 44(57.5%) with squamous cell carcinoma, 20(29.9%) with adenocarcinoma, 1(1.5%) with large cell carcinoma and 2(3%) with unverified carcinoma. The median age was 59(31-69) years. All patients completed the treatment as planned, except that 3 patients missed one cycle chemotherapy. There were 8(11.9%), 43(64.2%), 11(16.4%) and 4(6.0%) patients achieved complete response, partial response, stable disease and progressive disease respectively. The objective remission rate (ORR) is 76.1%. There were 23 patients (34.3%) with grade 3+4 neutropenia, 9(13.4%) with grade 3+4 anemia, and 10(14.3%) with grade 3+4 thrombocytopenia. Three patients (4.5%) developed grade 3 nausea/vomiting, 3 patients (4.5%) developed grade 3 acute esophagitis, grade 1+2 and 3 grade pneumonitis were observed in 8(11.9%), 12(17.9%) and 2(3.0%) patients respectively. One patient died of pneumonitis before efficacy evaluation. No grade 2 cardiovascular toxicity was observed. Up to the last follow-up, the median follow-up time of 26.8 months (range 1-69), 5-year disease-free and overall survival rates in Stage IIIA patients were 47.9% and 54.8% respectively. Conclusion: Chemo-sensitivity could be evaluated using CD-DST after lung cancer surgery. CD-DST may contribute to individualized adjuvant chemotherapy for locally advanced lung cancer.

Keywords: drug sensitivity test, lung cancer, adjuvant chemotherapy

P2.02-026 MULTIVARIATE ANALYSIS TO PREDICT TUMOR RESPONSE AND OUTCOMES IN PATIENTS WITH RESECTED LUNG CANCER ACCORDING TO COLLAGEN GEL DROPLET-EMBEDDED CULTURE DRUG SENSITIVITY TEST
Masayoshi Inoue, 1Hajime Maeda, Yukiyasu Takeuchi, Kenjiro Fukuhara, Yasushi Shintani, Yasunori Funakoshi, Soichiro Funaki, Takashi Nogiri, Takashi Kusu, Hidenori Kumamoto, Toru Kimura, Meinschon Okumura
1Division of Thoracic Surgery, Department of Surgery, Kyoto Prefectural University of Medicine, Kyoto City, Japan; 2Tsumoto City Hospital, Tsumoto City, Japan; 3Kurume University Graduate School of Medicine, Kurume, Japan; 4Zakarazuka City Hospital, Takakuzu City, Japan; 5Osaka University Graduate School of Medicine, Suita, Osaka, Japan; 6Osaka General Medical Center, Osaka City, Japan; 7Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka City, Japan.

Background: The efficacy of adjuvant chemotherapy for locally advanced lung cancer cannot be assessed during the treatment, since there is no measurable lesion after surgical resection. We conducted a prospective clinical trial according to the results of drug sensitivity test with an aim to individualize adjuvant chemotherapy. Methods: Patients with resectable cStage IB-IIIA non-small cell lung cancer were registered between 2005 and 2010. Collagen gel droplet-embedded culture drug sensitivity test (CD-DST) was performed on fresh surgical specimen. The clinical utility and prognostic outcome of adjuvant chemotherapy with carboplatin/paclitaxel in patients who showed chemo-sensitivity on CD-DST were evaluated. The primary endpoint was disease-free survival, and the secondary endpoints were overall survival and adverse effects during chemotherapy. Results: Among 92 registered patients, 87 (Stage IIB in 54, IIA in 4, IIB in 10, IIB in 10) were eligible and were included in the analysis. All patients were followed up for more than 5 years. The median age was 66 years old. The success rate of CD-DST was 87% and chemo-sensitivity to carboplatin and/or paclitaxel was observed in 75% of patients. Adjuvant chemotherapy was completed in 70% and the 5-year disease-free and overall survival rates were 68% and 82%, respectively. The 5-year disease-free and overall survival rates in Stage II–IIIA patients were 58% and 75%, respectively. As for the adverse effects during adjuvant chemotherapy, grade 4 neutropenia was found in 13%. Conclusion: Chemo-sensitivity could be evaluated using CD-DST after lung cancer surgery. CD-DST may contribute to individualized adjuvant chemotherapy for locally advanced lung cancer.

Keywords: drug sensitivity test, lung cancer, adjuvant chemotherapy

P2.02-027 A RANDOMIZED PHASE II TRIAL OF S-1 PLUS CISPLATIN OR DOCETAXEL PLUS CISPLATIN WITH CONCURRENT THERAPEUTIC RADIOTHERAPY FOR STAGE III NSCLC: TORG1018
1Division of Respiratory, Neurology, and Rheumatology, Department of Internal Medicine, Kurume University School of Medicine, Kurume, Japan; 2Thoracic Oncology Research Group, Yokohama, Japan.

Background: Concurrent chemoradiotherapy (CCRT) is the current standard treatment for inoperable stage III non-small cell lung cancer (NSCLC), and a clearly superior regimen has not yet been identified. This study was conducted to evaluate cisplatin with 5(1) or docetaxel (DP) with concurrent thoracic radiotherapy in patients with inoperable stage III NSCLC. Methods: In this open-label, non-comparative phase II trial, patients with inoperable stage IIIA/B NSCLC were randomized (1:1) to SP (S-1 40 mg/m² on days 1-21) or DP (docetaxel 50 mg/m² on days 1-21 and cisplatin 60 mg/m² on days 1 and 29). The primary endpoint was the 2-year overall survival (OS) rate, and the secondary endpoints were OS, progression-free survival (PFS), toxicity profile, dose intensity and objective response rate (ORR). Results: Between May 2011 and August 2014, 110 patients from 19 institutions were enrolled. Finally, 106 patients (56 in each arm) were evaluated for efficacy and safety. The patient characteristics were: male/female, 83/23; median age, 65 (range 42-74) yr; performance status 0/1, 59/47; II/IIIA, 59/47. After a median follow-up of 23.1 months, ORR and median PFS were 71.7% (95%CI: 57.7-83.2) and 11.5 months (95%: 9.00-14.1) in the SP arm, and 67.9% (95%CI: 53.7-80.1) and 17.2 months (95%: 9.62-24.0) in the DP arm, respectively. Grade 3-4 leukopenia (34.0%/62.3%) and neutropenia (28.3%/56.6%) were significantly higher in the DP arm than in the SP arm. Incidences of non-hematological toxicity including febrile neutropenia, anorexia, nausea, diarrhea, radiation pneumonitis and esophagitis tended to be high in the DP arm. No treatment-related death occurred. Conclusion: At this preliminary stage, it appears that although the DP arm may have more toxic effects than the SP arm, it has a
Abstracts

POSTER SESSION - P2.02: LOCALLY ADVANCED NSCLC MULTIMODALITY TREATMENT - TUESDAY, DECEMBER 6, 2016

P2.02-028 A PHASE II/I STUDY OF CARBOPLATIN, PEMETREXED, AND CONCURRENT RADIATION THERAPY FOR PATIENTS WITH LOCALLY ADVANCED NSCLC. CJLS0912
Naohiko Murata1, Masashi Kondo1, Chiyoe Kitagawa1, Hideo Saka1
1Respiratory Medicine, Japanese Red Cross Nagoya Daini Hospital, Nagoya/Japan, 2Respiratory Medicine, Nagoya University, Nagoya/Japan, 3Respiratory Medicine, National Hospital Organization Nagoya Medical Center, Nagoya/Japan

Background: A combined concurrent therapy with a platinum-based regimen and radiation is recognized as a standard for patients with unresectable stage III lung cancer. Though combined therapy has improved survival, little improvement was reported after that for decades. Pemetrexed is a new generation drug which is widely recognized as a safe and effective agent for patients with stage IV lung cancer. Moreover pemetrexed is expected to have a synergistic effect with radiation in vitro study. The purpose of this study was to investigate the safety and toxicity profile of a regimen of pemetrexed and carboplatin (Pem/CBDCA) plus concurrent thoracic radiotherapy (TRT) followed by consolidation therapy with Pem/CBDCA for Japanese patients with unresectable non-small cell lung cancer (NSCLC). Methods: We planned a multi-institutional open clinical phase II/I trial of Pem (500 mg/m²)/CBDCA (Adriamycin) and concurrent TRT for patients with stage IIIA/IIIB NSCLC. Patients were administered two cycles of Pem/CBDCA with three-weeks interval and delivered 60 Gy radiotherapy in 30 fractions concurrently. Additional two cycles of Pem/CBDCA with a three-weeks interval were administered after the safety of concurrent therapy was confirmed. Regarding a phase I study, we confirmed a safety of this therapy every three consecutive patients. In case that three or more DLTs in first six patients occurred, a dose of CBDCA was to be decreased from AUC 5 to 4. We planned to enroll thirty patients in this study in total of phase I and II. Results: Median follow-up period was 27.4 months. DLTs were observed in two out of six patients. This fulfilled preplanned criterion to conclude therapeutic dose. The most frequent non-hematologic adverse event was esophagitis (66.7%). Neutropenia was observed rather frequently (83.3%), but no patients developed febrile neutropenia. As to two cases of DLT, one patient experienced grade 3/4 radiation pneumonitis. The other patient presented prolonged leukocytopenia. Other four patients completed scheduled therapy. Five patients (83.3%) got PR. Two-year survival was 100%. Disease progression was observed in three patients during study period. Because of slow accrual, phase II study was not conducted. Conclusion: Present therapy is feasible for Japanese patients with unresectable stage III NSCLC. Trial registration: UMIN000008426

Keywords: Chemoradiotherapy, Safety, pemetrexed

POSTER SESSION - P2.02: LOCALLY ADVANCED NSCLC MULTIMODALITY TREATMENT - TUESDAY, DECEMBER 6, 2016

P2.02-030 CONCURRENT CHEMOTHERAPY FOLLOWING CONCURRENT CHEMORADIATION FOR STAGE III NON-SMALL CELL LUNG CANCER: A BRAZILIAN MULTICENTRIC COHORT
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Background: Locally advanced stage III grossly accounts for 25% newly diagnosed non-small cell lung cancer (NSCLC) cases. Although some patients (pts) are amenable to surgical resection, most will be treated with concurrent chemoradiation (CRT), whilst the addition of consolidation chemotherapy (CC) is still a debatable topic. We decided to look into the impact of CC in stage III NSCLC Brazilian pts treated in the daily clinical practice. Methods: We retrospectively collected data of stage III NSCLC pts treated in five different Brazilian cancer institutions from Jan/2007 to Dec/2011, whom have received CRT followed or not by CC. Eligible pts were ≥ 18yo and must have been treated with cisplatin or carboplatin plus etoposide, paclitaxel or vinorelbine, concurrently with thoracic irradiation (RT). Patients treated with surgery or neoadjuvant chemotherapy were excluded. Primary endpoint was overall survival (OS) from the date of diagnosis. Association between CC and clinical variables and demographics were evaluated by Pearson’s Chi-square test (Χ²). Survival curves were generated by Kaplan-Meier method and compared by log-rank test. Univariate and multivariate analysis were made using Cox proportional model (CPM). P-values 0.05 were deemed statistically significant. Results: We collected data from 165 pts. Median age was 60yo (range: 27.7-90) and most pts were male (65.9%), Caucasian (77.9%), current or former smoker (93.3%), and staged as IIIB (52.7%). Adenocarcinoma was the most common histologic type (47.9%). Weight loss>5% and ECOG-PS 2 were more prevalent than expected. We observed no statistically significant difference in OS between patients treated or not with CC (p=0.21), although 3-year OS rate was numerically higher in CC pts (40% vs. 31%). Median OS in was 24 and 25 months in CC and non-CC groups, respectively (HR 1.408, 95%CI 0.814-2.434). A significant increase in the delivered RT dose ≥ 65 Gy was the only variable associated with improved survival (HR 0.617, 95%CI 0.419-0.909, p=0.012). Conclusion: CC did not improve OS in stage III NSCLC patients after concurrent CRT. RT dose ≥ 65 Gy was not associated with improved survival.
Background: Although the efficacy of postoperative adjuvant cisplatin (CDDP)-based chemotherapy, such as the combination of CDDP and vinorelbine (VNR) has been established for surgically resected non-small cell lung cancer (NSCLC), there has been some reports about the survival data of Asian patients treated with the combination of CDDP and VNR as adjuvant chemotherapy. Methods: We retrospectively have evaluated patient compliance and the safety of adjuvant chemotherapy conducted by the Kaplan-Meier method to assess the time to death or relapse. Results: One hundred surgically resected NSCLC patients were included in this study. The characteristics of the patients were as follows: median age 63 years (range: 36–74); female 34%; never smokers 20 %; histology non-squamous/squamous cell carcinoma 73%/ 27%; EGFR mutation mutant/wild 19%/23%/58%. Pathological stages IIA/IIB/IIIA were observed in 31/22/47%. The median time from surgical resection to the start of adjuvant chemotherapy was 44 days (range: 25–79 days). Median follow up was 5.6 years (range, 3.8 – 9.7 years). The five-year OS rate was 73% and the 2-year OS rate was 93%. The five-year RFS rate was 53% and the 2-year RFS was 62%. A univariate analysis of prognostic factors showed that patient characteristics (gender, histology, pathological stage) and dose intensity of cisplatin were not significantly associated with OS. Conclusion: Our results suggested that the prognosis of surgically resected NSCLC patients, who were treated with the combination of CDDP and VNR as adjuvant chemotherapy might be better than previous results of adjuvant chemotherapies for NSCLC patients. This result can be influenced by the advances of diagnostic and surgical procedures, and the efficacy of chemotherapy including molecular target therapies.

Keywords: Cisplatin, non-small cell lung cancer, adjuvant chemotherapy, survival

P2.02-032 INDUCTION HISTOLOGY-BASED COMBINATION CHEMOTHERAPY FOR ELDERLY PATIENTS WITH INOPERABLE NON-SMALL CELL LUNG CANCER (NSCLC)

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Background: SABR is an acceptable treatment of elderly patients with inoperable stage II NSCLC; for the stage III, sequential chemoradiotherapy may be appropriate, since it is better tolerated than concurrent chemoradiotherapy. Methods: In a prospective phase II not randomised study, patients aged 70 years or more with inoperable stage III A and IIIB histologically confirmed squamous cell carcinoma (SCC) or adenocarcinoma NSCLC and ECOG performance status (PS) 0-2, were treated with 3 cycles of induction chemotherapy according to their histology followed by definitive radiotherapy or possible surgery in selected cases. Chemotherapy regimens included: carboplatin at AUC 5 i.v. plus gemcitabine 1000 mg/m² i.v. on days 1,8 or pemetrexed 500 mg/m² i.v. every 21 days in patients with squamous or adenocarcinoma, respectively. Primary endpoint was activity as defined by the overall response rate (ORR) following induction chemotherapy and overall survival (OS); secondary endpoints included feasibility outcome (i.e., toxicity, rate of definitive radiotherapy, chemotherapy dose reduction or withdrawal) and progression-free survival (PFS). Results: Twenty-seven patients, 23 males, 4 females, with a median age of 74 years (range, 70-80), PFS/0+1 in 9/5 (33.5%) or 2 in 3 (11%) and median of 2 (range, 0-5) active comorbidities requiring medical treatment were treated. Fourteen patients (52%) had an adenocarcinoma and were treated with carboplatin and pemetrexed, 13 a SCC (42%) with carboplatin and gemcitabine. Eight patients (30%) had a stage IIIA, 19 patients (70%) a stage IIIB. The median cycle of chemotherapy was 3 (range, 1-4). Dose reduction or withdrawal was required in 2 and 3 patients, respectively (18%). ORR was 46% (in 12 of 26 assessable patients); 5 patients with a SCC (42%) and 7 patients with an adenocarcinoma (50%). SD and PD were reported in 4 (15%) and 10 (38%) patients, respectively. Twelve patients (44%) were subsequently treated with radiotherapy, 8 (42%) with stage IIIB and 4 (50%) with stage IIIA. Two patients (7%) with stage IIIA disease underwent lobectomy. With a median follow-up of 10.2 months, 9 patients (33%) were alive and progression-free; median OS and PFS data will be shown. G1-2 neutropenia, anemia, nausea/vomiting and diarrhea were the most frequent toxicity observed in 10% of patients and up to 45% for neutropenia. G3-4 neutropenia, anemia, thrombocytopenia and fever was reported in one patient each (4%), G3 anemia in 2 patients. Conclusion: In a broad elderly NSCLC population induction histology-based chemotherapy seems to be active and feasible in selected patients.

Keywords: locally advanced, induction chemotherapy, elderly, NSCLC
P2.02-036 DOUBLE PLASTY OPERATION; A PROCEDURE WITH PULMONARY ARTERIOPLASTY AND BRONCHOPLASTY AGAINST CENTRALLY LOCATED NON-SMALL CELL LUNG CANCER
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Background: Against non-small cell lung cancer (NSCLC) centrally located and involving both artery and bronchus, resection with pulmonary arterioplasty and bronchoplasty are effective to avoid pneumonectomy and keep activity of daily life of patients. To elucidate the complications, prognosis, association with induction therapy and surgical technique of this complex operation with double plasty, we report the series in our institute. Methods: 45 patients underwent bronchoplastic lobectomy due to NSCLC in our institute from January 2002 to December 2012 and 18 patients of these were received double plasty surgery (40.0%). As preoperatively, 4 received chemotherapy (22.2%), 2 received chemoradiotherapy (11.1%) and 1 received radiotherapy (5.6%). Results: 17 patients (94.4%) were added pedicled flap attachment on the bronchial Anastomosis for reinforcement and prevention of contacting artery and bronchus. 10 of 16 patients (62.5%) who needed total pulmonary artery clamp were heparinized during clamping. No intraoperative and 30-day postoperative mortality was observed. Complications occurred in 7 patients (38.9%) and 1 patient died in 3 months after the surgery due to empyema which was induced by lung fistula developed with the influence of preoperative radiotherapy. Other 6 patients were all recovered from the complications without any sequel. There were no complications about bronchial anastomosis and the site of arterio-plasty. During observation period, 5 patients developed lung cancer recurrence and they all died. The overall 5-year survival rate was 65.7% although advanced stage. Conclusion: For locally advanced NSCLC, double plasty surgery can be valuable alternative to resect NSCLC completely and preserve lung function. Complications and overall survival rate are acceptable.

Keywords: Pedicled flap, non-small cell lung cancer, Double plasty
since we have demonstrated radiation sensitization by erlotinib in a preclinical setting using a mouse model. Methods: 48 patients with stage III NSCLC, PS 0-1, received radiotherapy (63 Gy/35 fractions) on Monday-Friday, with chemotherapy (paclitaxel 45 mg/m², carboplatin AUC-2) on Mondays, for 7 weeks. All patients also received EGFR-TKI erlotinib (150 mg orally 1/day) on Tuesday–Sunday for 7 weeks followed by consolidation paclitaxel–carboplatin. The primary endpoint was time to progression; secondary endpoints were overall survival (OS), toxicity, response, and disease control and whether any endpoints differed by EGFR mutation status. Results: 46 out of 48 patients were evaluable for response; 40 were former or never smokers and 41 were evaluated for EGFR mutation status: 37 were wild-type and 4 were found to have mutation (3 exon 19 deletion, 1 exon 21 mutation). Median time to progression was 14 months and did not differ based on EGFR mutation status. Toxicity was acceptable: no grade 5 toxicity, 1 grade 4, and 1 grade 3. Twelve (26%) had complete responses (10 with wild type (wt) and 2 with mutation (mt) and 1 unknown). At 73.5 months median follow-up (range 66.2–93.7 months), 2 and 5 year OS rates were 67.4% and 36.25%; there were no significant differences by mutation status. Twelve patients had no progression and 34 had local and/or distant metastasis. All 4 patients with EGFR mutation had local control. Eleven of 27 patients failed in the brain (7 wt, 3 mt and 1 unknown). Conclusion: Toxicity was acceptable and OS was promising, but time to progression did not meet expectations. The prevalence of distant failures underscores the need for effective systemic therapy. Those patients with EGFR mutation might need induction erlotinib followed by local treatment when they fail locally in the lung or brain which is fairly frequent among EGFR mutated patients.

Keywords: lung cancer, Non-small-cell, Erlotinib, chemoradiation

Poster Session 2 - P 02. Locally advanced NSCLC: multidisciplinary treatment – Tuesday, December 6, 2016

P 02.02-038 Surgical Outcome of Stage IIIA N2-CN2/PN2 Non-Small Cell Lung Cancer

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Background: Treatment for patients with confirmed mediastinal lymph node involvement (N2/N3A) is still a controversial issue. In this study, we evaluated the effect of surgical outcome in patients with clinical(c) stage IIIA N2 non-small-cell lung cancer (NSCLC) pathologically proven N2/N2(N2) before surgery. Methods: The subjects selected for analysis were 63 patients with Stage IIIA-c2N2/pN2 NSCLC who underwent surgical complete pulmonary resection among 1340 cases receiving surgical resection for NSCLC at Nagasaki University between January 2000 and July 2013. Of these 63 cases, 32 patients pathologically proven N2-positive stage III NSCLC underwent induction therapy. As for the induction therapy, 21 cases had chemotherapy, and 11 cases had induction erlotinib followed by local treatment when they fail locally in the lung or brain which is fairly frequent among EGFR mutated patients.

Keywords: lung cancer, Non-small-cell, Erlotinib, chemoradiation

Poster Session 2 - P 02. Locally advanced NSCLC: multidisciplinary treatment – Tuesday, December 6, 2016

P 02.02-040 Phase 3 Randomized Low-Dose Paclitaxel Chemoradiotherapy Study for Locally Advanced Non-Small-Cell Lung Cancer

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Background: Concurrent chemoradiotherapy (CCRT) is the standard treatment for locally advanced non-small cell lung cancer (LA-NSCLC), but is associated with poor chest tumor control. Here we report results of a randomized phase 3 study comparing two CCRT regimens in improving chest tumor control by low-dose paclitaxel chemoradiation for LA-NSCLC. Methods: Due to the logistics of the local referral pattern, the study was designed to enroll patients with stage IIIA-III NSCLC who had completed 2-4 cycles of full-dose chemotherapy. One hundred thirty four were randomized to either Arm 1 (paclitaxel at 15 mg/m² and Carboplatin AUC 2, q3wk for locally advanced were treated on an individual basis, remission induction was observed and pts are on 1st gen TKI (Erlotinib d4-20 mg/day p.o. or Gefitinib 250 mg d4-20 at each cycle). PR was achieved after 2 cycles in all patients. All 5 patients were resected, response grade III or IV was remarked in mediastinal lymph nodes (#1-4). Pt. #5 had progression grade III. All 5 patients received adjuvant radiotherapy of the mediastinum. One patient died of secondary cancer (rectal cancer) 52 months after diagnosis of NSCLC. 4 pts are alive for 20 to 24 months. 3 patients had 2nd isolated CNS metastases and 12 months after primary diagnosis which were treated by surgery and/or radiosurgery. Pts 2, 4 and 5 relapsed with distant mets. No resistance mutation was observed and pts are on 1st or 2nd gen. TKI therapy. A phase II trial (Neolintal) trial is currently under way in 9 German centers in stages II and III supported by AstraZeneca Pharmaceuticals. Preliminary results of these patients will be presented at the meeting. Conclusion: Intercalated TKI therapy is a promising treatment in patients with EGFR mt+ locally advanced NSCLC that is pursued in a prospective phase II trial in Germany. CNS mets seems to be the primary site of relapse in most patients.

Keywords: EGFR mutation, molecular diagnostic, NSCLC

Poster Session 2 - P 02. Locally advanced NSCLC: multidisciplinary treatment – Tuesday, December 6, 2016

P 02.02-039 Interclouded EGFR and Chemotherapy in Locally Advanced NSCLC with EGFR Mutations: Data on 5 Patients

AND CLINICAL STUDY

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Background: EGFR TKI’s are standard of care in patients with EGFR mt+ NSCLC IV. However, induction concepts including intercalated TKI/CX, in locally advanced NSCLC with EGFR mutation including TKI have not been studied extensively. This concept was used as induction regimen in 5 patients with activating EGFR mutations in stages IIIA and IIIb and is now carried on in a phase II study (Neointical). Methods: Patients with EGFR mt+ NSCLC locally advanced were treated on an individual basis, remission induction was measured by RECIST 1.1, regression grading by jencker criteria. Results: 3 female never smokers (pt#1, #3, #5), 59, 62, 62 y.o. 2 male light smokers (pt#2 and #4), 58 and 69 y.o. were diagnosed with with TTF1+ adenoscarcomomas of the lung, 2 with exon 21 L858R (#1, #2) and 3 with exon 19 deletions (#3, #4, #5). 4/5 patients (#1-#4) carried p53 mutations. Tumor stages were IIIb in pts. #1, #2, #3, #4 pt, pT3a, pN0, pM0, oligometastatic GMD with one organ involved pt. #4, induction therapy was TKI (Erlotinib or Gefitinib) days 1-12 to 1, followed by 3 cycles of chemotherapy (Docetaxel 75 mg/m² d1/Epiplatin 50 mg/m² d1-2-dq22 or Paclitaxel 200 mg/ m² and Carboplatin AUC 6 d1, q22) in combination with TKI (Erlotinib d4-20 mg/die p.o. or Gefitinib 250 mg d4-20 at each cycle). PR was achieved after 2 cycles in all patients. All 5 patients were resected, regression grade III or IV was remarked in mediastinal lymph nodes (#1-4). Pt. #5 had regression grade III. All 5 patients received adjuvant radiotherapy of the mediastinum. One patient died of secondary cancer (rectal cancer) 52 months after diagnosis of NSCLC. 4 pts are alive for 20 to 24 months. 3 patients had 2nd isolated CNS metastases and 12 months after primary diagnosis which were treated by surgery and/or radiosurgery. Pts 2, 4 and 5 relapsed with distant mets. No resistance mutation was observed and pts are on 1st or 2nd gen. TKI therapy. A phase II trial (Neointical) trial is currently under way in 9 German centers in stages II and III supported by AstraZeneca Pharmaceuticals. Preliminary results of these patients will be presented at the meeting. Conclusion: Intercalated TKI treatment is a promising treatment in patients with EGFR mt+ locally advanced NSCLC that is pursued in a prospective phase II trial in Germany. CNS mets seems to be the primary site of relapse in most patients.

Keywords: paclitaxel, chemoradiation, non-small cell lung cancer, radiosensitization

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The patients without lymph-node involvement (N0) had longer survival than factors. Conclusion: The OS of patients with squamous lung carcinoma was T stage (\(P = 0.000\)), smoking index (\(P = 0.000\)) analyses were carried out for overall survival (OS) and the presence of residual carcinoma at the incised margin, intravascular cancer, and pleural effusion were significantly related to patient survival (\(P < 0.05\)). On multivariate analysis, the smoking index (\(P = 0.000\)), T stage (\(P = 0.005\)), and N stage (\(P = 0.000\)) were independent prognostic factors. Conclusion: The OS of patients with squamous lung carcinoma was low. The survival rates gradually decreased as patients’ ECOG-PS declined. The patients without lymph-node involvement (N0) had longer survival than those with N1 and N2 lymph-node involvement. Both OS and disease-free survival are worse in SCC of the lung than for NSCLC in general. At present, we still depend on surgical intervention for squamous NSCLC; there is an unmet need for novel effective therapies.

Abstracts

POSTER SESSION 2 – P2.02: LOCALLY ADVANCED NSCLC MULTIMODALITY TREATMENT – TUESDAY, DECEMBER 6, 2016

P2.02-041 THE IMPACT OF SURGICAL RESSECTION AFTER CONCURRENT CHEMOTHERAPY AND HIGH DOSE (61 Gy) RADIATION IN STAGE IIIA/N2 NON-SMALL CELL LUNG CANCER

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Background: Locally advanced stage IIIA non-small cell lung cancer with N2 disease is the most advanced stage at which cure can be achieved, but more than 60% of patients eventually die from their disease. For patients with stage IIA/N2 disease, two standard treatment options are offered: definitive concurrent chemoradiotherapy or surgery combined with chemoradiotherapy. We aimed to investigate the role of surgery after concurrent chemotherapy and high dose radiation in patients with N2 disease.

Methods: Between January 2011 and December 2015 eligible patients had pathologically proven stage II/IIIA/N2 non-small-cell lung cancer and were prospectively recorded. Those in the chemoradiotherapy group received three cycles of neoadjuvant chemotheraphy (AUC2 cartoplatin and docetaxel 85 mg/m² docetaxel) and concurrent radiotherapy with 61.2 Gy in 34 fractions over 3 weeks followed by surgical resection, and those in the control group received definitive chemoradiotherapy alone. All patients in two groups were proven to have no N2 disease after chemoradiotherapy. Results: A total of 58 patients were enrolled, of whom 21 received chemoradiotherapy followed by surgical resection and 37 had chemoradiotherapy only. Median overall survival was 35 months (95% CI 10.5 – 44.9) in the chemoradiotherapy + surgery group and 20.3 months (4.5 – 38.6) in the control group (\(P = 0.03\)). Median overall survival was 37 months (95% CI 22.6 – 50.0) with radiotherapy, compared with 26.2 months (19.9 – 52.1) in the control group.

Keywords: N2 disease, Stage IIIA, concurrent chemoradiotherapy, Surgical resection

POSTER SESSION 2 – P2.02: LOCALLY ADVANCED NSCLC MULTIMODALITY TREATMENT – TUESDAY, DECEMBER 6, 2016

P2.02-042 SURGICAL MANAGEMENT OF SQUAMOUS CELL CARCINOMA OF THE LUNG: SURVIVAL AND FUNCTIONAL OUTCOMES

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Background: Squamous cell carcinoma (SCC) of the lung is a unique clinical and histologic category of non-small-cell lung cancer (NSCLC) and accounts for about 30% of all lung cancer. Surgical intervention is the principal treatment for SCC. The purpose of this study was to evaluate the survival rates for surgical treatment of squamous NSCLC and the prognostic patient factors. Methods: We retrospectively evaluated the files of 170 patients with squamous NSCLC who were treated at the Thoracic and Cardiovascular Surgery, Tianjin Medical University General Hospital, between January 2008 and December 2011. Univariate (Cox regression analysis) and multivariate (likelihood ratio) analyses were carried out for overall survival (OS) and the median survival duration. A \(P\)-value of < 0.05 was defined as significant.

Results: The median OS was 29 months, the 1-year OS was 78.2%, and the 5-year OS was 15.3%. On univariate analysis, the Eastern Cooperative Oncology Group Performance Status (ECOG-PS) score; tumor (T) stage; node (N) stage; type of surgery; type of lymphadenectomy; and the presence of residual carcinoma at the incised margin, intravascular cancer, and pleural effusion were significantly related to patient survival (\(P < 0.05\)). On multivariate analysis, the smoking index (\(P = 0.002\)), ECOG-PS (\(P = 0.000\)), T stage (\(P = 0.005\)), and N stage (\(P = 0.000\)) were independent prognostic factors. Conclusion: The OS of patients with squamous lung carcinoma was low. The survival rates gradually decreased as patients’ ECOG-PS declined. The patients without lymph-node involvement (N0) had longer survival than those with N1 and N2 lymph-node involvement. Both OS and disease-free survival are worse in SCC of the lung than for NSCLC in general. At present, we still depend on surgical intervention for squamous NSCLC; there is an unmet need for novel effective therapies.

Keywords: non-small cell lung cancer, Vaccine, stage III
Background: Medialinal nodal downstaging is an important prognostic factor of neoadjuvant concurrent chemoradiotherapy (CRT) for stage IIIA-N2 non-small cell lung cancer (NSCLC) and the role of tridomal treatment remains controversial in patients with persistent N2 disease. We aimed to investigate survival outcomes based on the extent of pre-CRT nodal involvement and mediastinal nodal response in patients who underwent neoadjuvant CRT for stage IIIA-N2 NSCLC. Methods: A retrospective review of patients with N2 disease who underwent neoadjuvant CRT followed by surgery at our institution was performed and survival outcomes were compared according to the extent of pre-CRT medialinal nodal involvement and mediastinal nodal response. Extensive lymph node involvement was defined as a maximal axis diameter of lymph nodes > 2 cm measured at computed tomography or involvement of 2 or more mediastinal lymph node stations. Results: From 2003 to 2013, 407 patients underwent curative-intent surgery after neoadjuvant CRT for NSCLC with pathologically proven N2 disease. The mean age was 59 years (314 men, 77%) and histologic type included adenocarcinoma in 233 patients (57%), squamous cell carcinoma in 141 (35%), and large cell carcinoma in 11 (2.7%). Seventy-nine patients (19%) had extensive N2 disease on pre-CRT imaging tests. The extent of surgery included lobectomy in 311 patients (76%), pneumonectomy in 43 (11%), and sleeve resection in 15 (3.7%). Post-CRT pathologic nodal status was ypN0 in 155 patients (38%), ypN1 in 56 (14%), and ypN2 in 196 (48%). With a mean follow-up of 41 months, median overall survival (OS) and recurrence-free survival (RFS) were 73 months and 18 months, respectively. The 5-year OS and RFS rates were 61% and 62% in ypN1 and 40% and 13% in ypN2, respectively (OS, p=0.0032; RFS, p<0.0001). For patients with ypN0, the 5-year OS and RFS rates were 60% and 52% in extensive N2 disease and 61% and 40% in non-extensive N2 disease, respectively (OS, p=0.8106; RFS, p=0.1218). For patients with ypN2, the 5-year OS and RFS rates were 22% and 12% in extensive N2 disease and 4% and 12% in non-extensive N2 disease, respectively (OS, p=0.0403; RFS, p=0.4842). Conclusion: Pre-CRT non-extensive N2 disease was associated with better OS, but was not with better RFS in patients with persistent N2 disease. Patients who achieved medialinal downstaging showed acceptable OS and RFS regardless of N2 extensiveness. Considering heterogeneity of N2, the indication of neoadjuvant CRT needs to be differentiated according to the extent of pre-CRT nodal involvement and post-CRT mediastinal nodal response.

Keywords: neoadjuvant CRT, non-small cell lung cancer, Persistent N2, Bulky nodal involvement

P2.02-045 PROGNOSTIC VALUE OF METABOLIC FDG-PET RESPONSE IN LOCALLY ADVANCED NSCLC: A LITERATURE REVIEW

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Background: It is still a matter of debate whether metrics of metabolic imaging by 18F-Fluorodeoxyglucose positron emission tomography (18F-FDG-PET) predict clinical outcome in non-small cell lung cancer (NSCLC). Pretreatment FDG uptake in the primary tumor has been shown to be a prognostic factor for survival. The prognostic role of FDG-PET in the evaluation of tumor response remains unclear and controversial. Hence, we conducted a comprehensive literature review to assess the prognostic value of FDG-PET/CT response monitoring along multimodality treatment in patients with locally advanced NSCLC. Methods: A systematic search of studies published in PubMed was performed using the keywords “positron emission tomography” or “PET,” “non-small cell lung cancer,” and “response” or “outcome.” References from adequate articles were checked for studies not retrieved by the search strategy. Inclusion criteria were: studies limited to locally advanced NSCLC containing ≥60% stage III patients, studies in which response monitoring with FDG-PET or PET/CT was performed, and studies that reported survival data. Results: Twenty-two studies (median 47 patients, range 15-545) published between 1998 and 2016 were included in the analysis. Ten studies used PET alone while recent trials used integrated PET/CT. PET based response evaluation was performed either after neoadjuvant chemotherapy prior to surgery or radiotherapy either after radical treatment consisting of chemotherapy and radiotherapy. Eight studies specifically addressed the prognostic value of early metabolic response measurement, either during induction chemo/radiotherapy (n=2) either early in the course of radical (chemo)radiotherapy (n=6). A heterogeneity between the studies was observed regarding timing of the repeat PET, thresholds to define metabolic response, and metrics of metabolic FDG imaging such as MRgL (metabolic rate of glucose), Total Lesion Glycolysis (TLG), Standardized Uptake Value (SUVmax, SUVpeak, SUVmean or Metabolic Tumor Volume (MTV)). All studies showed a significant correlation between either the change in FDG uptake or the residual FDG uptake within the primary tumor and survival. Conclusion: Posttreatment FDG-PET/CT has been considered as a useful tool in determining prognosis and guiding therapy for patients with locally advanced NSCLC. Before implementation in routine clinical practice, there is however a need for standardization of PET data acquisition and analysis and a validation of a single definition for metabolic tumor response.

Keywords: outcome, locally advanced non-small cell lung cancer, FDG-PET, response

P2.02-046 PROGNOSTIC VALUE OF EARLY TUMOR REGRESSION DURING CHEMO-RADIOThERAPY IN LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER

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Background: Volumetric changes are observed on serial cone-beam computed tomography (CBCT) images obtained for image-guidance throughout the course of radical radiotherapy for non-small cell lung cancer (NSCLC). This study aims to a) examine whether the magnitude of tumor regression is correlated with disease control and survival; b) explore the potential difference between adenocarcinoma and non-adenocarcinoma NSCLC subtypes. Methods: In a previous study from our institution, primary tumor volumes were assessed on weekly CBCT images of 60 NSCLC patients treated with radical radiotherapy from January 2006 to June 2007. We performed a retrospective review of these patients, documenting patient-, tumor-, treatment-related and outcome data. Outcome measures included loco-regional failure free survival (LRFFS), distant failure free survival (DFS), disease free survival (DFS) and overall survival (OS), which were calculated using Kaplan-Meier method. Univariable analysis (UVA) and multivariable analysis (MVA) were performed using Cox regression model. Further analysis was performed for the adenocarcinoma and non-adenocarcinoma subgroups. Results: Forty-five patients with locally advanced NSCLC were included in this study. Median follow-up was 22.1 months for all patients, and 90 months for alive patients (range: 0.2-108). The distribution of 7th ed. AJCC stage as follows: stage I 8.3%, II 16.7%, IIIA 6.7%, IIIB 24.6%. Twenty-six patients (56.6%) had adenocarcinoma, while 25 patients (55.6%) had non-adenocarcinoma. Eighty-twelve patients (62.3%) received total radiation dose ≥ 60 Gy, 15 patients (33.3%) received 45 Gy as neoadjuvant therapy, and 2 patients (4.4%) received 58-59 Gy due to missed fractions. 23 patients (51.1%) had more than 30% regression by fraction 5 and 32 patients (71.1%) by treatment completion. In UVA, adenocarcinoma (p=0.03) was associated with better LRFFS; young age was associated with better LRFFS (p=0.02), DFS (p=0.048) and OS (p=0.04). In MVA, large regression by fraction 15 was associated with better DFS (p=0.047). For patients with adenocarcinoma, MVA showed that large regression by fraction 15 was associated with better DFS (p=0.01). DFS (p=0.01) and OS (p=0.02). For patients with non-adenocarcinoma, larger regression by treatment completion and trimodality therapy (radiation dose of 45 Gy) were associated with better LRFFS (p=0.02, 0.04). Conclusion: Evaluation of tumor regression on CBCT images during radiotherapy may be predictive of treatment response. Early tumor regression, as indicated by regression ≥ 30% by fraction 15, was associated with better DFS for all patients; and this was associated with better DFS, DFS and OS for the adenocarcinoma cohort. This observation may provide insight into when and how to best utilize adaptive radiotherapy.

Keywords: lung cancer, cone beam computed tomography, tumor volume regression
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Background: Induction chemoradiotherapy (CRT) and surgical resection is considered standard care for treatment of node negative Pancoast tumours. However, not all patients benefit from this approach and there are no well-defined preoperative parameters to identify patients for whom addition of surgery may be unnecessary due to local control with CRT alone. We investigated whether baseline FDG positron emission tomography (PET) scan parameters or changes post induction may predict complete pathological response (pCR) to CRT and hence obviate the need for subsequent resection. Methods: We conducted a retrospective review of our prospectively maintained single institution database with supplemental chart review to evaluate: PET, histopathological, and clinical outcome parameters in consecutive patients undergoing curative intent trimodality treatment of Pancoast tumours from 2001 to 2016. Metabolic parameters based on the standardized uptake values (SUV) were calculated including SUVpeak (maximum SUV value), SUV180 (peak tumour-to-liver ratio) and TGV (total glycolytic volume, mean SUV x tumour volume). Two pathologists independently reviewed specimens to assess percentage viable tumour in resected tumours. Results: Nineteen patients (10 Females), median age 61(42-75) yrs completed trimodality treatment with 45% in the majority of cases. Histopathological data was available for all patients. Of the 19 patients baseline PET was available in 15 and post induction PET in 13. Baseline SUVpeak < 9.4 was associated with pCR in 4/4 vs. 4/11 patients (p=0.03). A trend towards improved locoregional control with pCR did not reach significance. No PET measured parameter was associated with locoregional control. Baseline TGV > 441 was associated with reduced disease free survival (DFS) (2.7(0.7-10.5) vs. NR months (p=0.002), and overall survival (OS) 15.9(3.1-89.5) vs. NR months (p=0.04). No change in PET parameter measured post induction was associated with cPR, local recurrence, DFS or OS. Conclusion: Neoadjuvant chemotherapy is a feasible in resources constrained settings, result in major pathological response in a proportion of patients with locally advanced NSCLC. Major pathological response and post-surgery pathological N0/N1 status associated with improved DFS.

Keywords: Pancoast, pathological response, PET/CT, survival

Conclusion: Neoadjuvant chemotherapy is a feasible in resources constrained settings, result in major pathological response in a proportion of patients with locally advanced NSCLC. Major pathological response and post-surgery pathological N0/N1 status associated with good outcome

Keywords: predictors of outcome, neoadjuvant chemotherapy, Locally advanced NSCLC

P2.02-049 GENDER AND RISK OF CESSATION OF ORAL VINORELBEIN IN A RANDOMIZED TRIAL OF CONCURRENT CHEMORADIATION OF LOCALLY ADVANCED NSCLC

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Background: Concurrent chemo-radiation (CRT) is the treatment of choice for locally advanced NSCLC (LA-NSCLC) patients, but a number of patients do not full fill the course of chemotherapy, and this may decrease survival. The aim of this study is to evaluate the influence of gender on the risk of cessation of oral vinorelbine used as concurrent chemotheraphy in a prospective clinical trial of chemoradiation of LA-NSCLC (The NARLAL trial). Data on esophagitis has previously been published demonstrating that females were more sensitive
than males (Radiother.Oncol.2016;118:465). Methods: From 2009 to 2013, 117 patients with LA-NSCLC in performance status (PS) 0-1 entered a randomized phase II trial comparing 60 Gy with 66 Gy in 2 Gy fraction 5 days a week in 6 to 6.5 weeks, the current work with venous collaterals as fixed dose of 50 mg 3 times a week. The intended number of doses of venorelbin was 17 to 19 depending on the treatment arm. In each of the treatment arms, 12% of the patients received 15 doses of oral venorelbin or less; here designated as chemo-non-compliant. Results: In the NARAL trial 49 female and 68 males participated. The median age were 65.5 years in both gender (p=ns), the distribution of stage did not differ significantly among gender, and neither did PS, but females had significant less pretreatment weight than males; the median being 70.0 and 84.0 kg, respectively. Altogether, 10 (20%) females and 4 (6%) males were chemo-non-compliant (p=0.04). The females had significant more grade 4 esophagitis than men, and significant more women had a more than 5 pctl. weight loss, 15 (31%) compared with 7 (10%) in men (p<0.01). Chemo-non-compliance was associated with esophagitis grade 2 or more, and with weight loss >5%. In a logistic regression analysis of chemo-non-compliance only female and PS=1 was significant: Female OR=3.74 (95% CI 1.07; 13.1), p=0.017; PS 0-5.59 (95% CI 1.70; 18.4), p=0.005. Introduction age, weight, body surface area (BSA), current smoking, or stage were non-significant factors. Conclusion: Females have a significant larger risk than males of not fulfilling chemotherapy with oral venorelbin and to lose weight > 5% during concurrent chemoradiation of LA-NSCLC. This cannot be explained by women having smaller BSA or weight than males.

Keywords: Concurrent chemoradiation, Oral Venorelbin, gender, compliance

POSTER SESSION 2 – P02: LOCALLY ADVANCED NSCLC
PROGNOSTIC FACTOR – TUESDAY, DECEMBER 6, 2016

P2.02-050 GENDER AND SMOKING INFLUENCE ON NON SMALL CELL LUNG CANCER HISTOLOGY AND TNM STAGE IN A BRAZILIAN POPULATION
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Background: Smoking is the most important lung cancer risk factor, although its not known if this risk is equal between men and women. The objective of the study is to analyze gender and smoking influence on lung cancer in a Brazilian population who underwent surgery for non small cell lung cancer (NSCLC). Methods: The study population derives from the Sao Paulo Lung Cancer Registry, which began in 2014 and includes patients with NSCLC who underwent surgery with curative intention. Results:

<table>
<thead>
<tr>
<th>Gender</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>65.5</td>
<td>65.0</td>
</tr>
<tr>
<td>Weight</td>
<td>84.0</td>
<td>70.0</td>
</tr>
<tr>
<td>Stage</td>
<td>65%</td>
<td>64%</td>
</tr>
<tr>
<td>Histology Type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>55%</td>
<td>50%</td>
</tr>
<tr>
<td>Squamous</td>
<td>25%</td>
<td>21%</td>
</tr>
<tr>
<td>Bronchioloalveolar</td>
<td>9%</td>
<td>19%</td>
</tr>
<tr>
<td>Other</td>
<td>10%</td>
<td>7%</td>
</tr>
<tr>
<td>Smokers</td>
<td>70%</td>
<td>66%</td>
</tr>
</tbody>
</table>

Data of 423 patients were obtained from the registry and 12 cases were excluded due to incomplete data. Out of the 411 patients analyzed, 215(52%) were women. The resections performed were lobectomy in 324 cases (80%), pneumonectomy in 26(6%), bilobectomy 184(45%), segmentectomy 20(5%), and wedge resection in 17(3%). Women were more likely to be never smokers than men (see Table); furthermore, males smoked for a longer period and had higher load of tobacco consumption. There were no differences between genders with regard to NSCLC detection method. There was a substantially higher percentage of squamous-cell carcinoma in men than in women (27%/M, 17%/W, p=0.008), while adenocarcinoma and carcinoid tumors were more frequent in women (55%/W, 50%/M; 19%/W, 12%/M, respectively, p=0.008). However, when stratified by smoking, the difference in NSCLC histologic types by gender disappears. More women had early-stage NSCLC than men (64%/W, 54% M, p=0.04). In a multivariate analysis female gender was an independent factor for early stage NSCLC (OR=0.43, p=0.05), but there was no influence of age, smoking history and histologic type. Conclusion: Currently, more women than men have been operated on due to NSCLC in Brazil and women tend to present in earlier stages of disease. We also found a large difference in smoking habits between genders, which can explain the differences in their histologic profile.

Keywords: Adenocarcinoma, Lung cancer, Smoke, curative intention, lobectomy, Tumors

POSTER SESSION 2 – P02: LOCALLY ADVANCED NSCLC
PROGNOSTIC FACTOR – TUESDAY, DECEMBER 6, 2016

P2.02-051 PROGNOSTIC VALUE OF THE PRETREATMENT PERIPHERAL BLOOD MARKERS IN PATIENTS WITH NON-SMALL CELL LUNG CANCER
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Department of Respiratory Diseases, University Clinical Hospital Center Zagreb, Croatia

Background: Lung cancer is the leading cause of cancer-related mortality worldwide. Regarding histological types, non-small cell lung cancer (NSCLC) represents 80% of all cases. In majority of all cases, NSCLC patients have locally advanced or metastatic disease at the time of diagnosis. Currently there is no predictive markers with clinical utility to guide treatment decisions in NSCLC patients undergoing therapy. We have compared (median overall survival) before treatment (chemotherapy, radiotherapy or surgery) in patients with NSCLC regardless of the disease stage. Methods: Total of 1359 medical records of patients diagnosed with lung cancer Clinical hospital center Zagreb, Department of respiratory diseases Jordanovac during the year 2012 and 2013 were retrospectively collected and reviewed. Of that number, 1179 were NSCLC patients (all subtypes). We have analyzed normal and elevated biochemical markers: CRP (cut off value was 5.0 mg/L), leucocytes (cut of value was 10x10^9/L), platelets (cut of value was 424x10^9/L) and fibrinogen (cut off value was 4.1 g/L) in patients before treatment and calculated mOS (median overall survival). Since not all of 1179 patients performed pretreatment laboratory tests in our Department, we were unable to review laboratory findings of all diagnosed patients. mOS was measured and analyzed using the Kaplan-Meier and log-rank test. Results: We have found out that in case of elevated CRP and leucocytes values prior to treatment patients had lower mOS regardless of therapeutic modality. Additionally, elevated levels of fibrinogen and platelets do not affect mOS. From 1179 NSCLC patients, CRP was initially measured in 770. In 116 patients CRP was normal (<5mg/L) and in 654 elevated (>5mg/L). We have compared normal and elevated biochemical markers affects the prognosis of lung cancer remains elusive.

Keywords: Blood markers in NSCLC

POSTER SESSION 2 – P02: LOCALLY ADVANCED NSCLC
PROGNOSTIC FACTOR – TUESDAY, DECEMBER 6, 2016

P2.02-052 DOES DELAY FROM DIAGNOSIS TO START OF RADIOTHERAPY, OR MODIFIED COMORBIDITY SCORE IMPACT SURVIVAL IN CURATIVELY TREATED NON SMALL CELL LUNG CANCER
Jeremy Ruben1, Katherine Neville1, Andrew Haydon2, Sashendra Senth1

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POSTER SESSION 2 – P2.02: LOCALLY ADVANCED NSCLC
PROGNOSTIC FACTORS
TUESDAY, DECEMBER 6, 2016

P2.02-054 IMPACT OF PROGNOSTIC NUTRITION INDEX FOR
INDUCTION CHEMORADIOThERAPY FOLLOWED BY SURGERy IN
LOCALLY ADVANCED NON-SMALL LUNG CANCERS
Junichi Soh, Shinichi Toyooka, Kazuhiro Shiien, Hiromasa Yamamoto, Tsuyoshi Kurosaki, Kentaro Miyoshi, Shinti Otani, Seiichiro Sugimoto, Massoomi Yamane, Takahiro Oto, Susumu Kanazawa, Katsuyuki Kiura, Shinichiro Miyoshi
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Background: The preoperative nutritional and immunological statuses have an important impact in predicting the clinical outcome of surgery. Induction chemoradiotherapy (iCRT) followed by surgery is one of treatment options for locally advanced (LA) non-small cell lung cancers (NSCLCs) although there is a risk for increasing postoperative complications with protracted wound healing. A prognostic nutritional index (PNI), calculated using serum albumin levels and peripheral lymphocyte count, has been used to predict the clinical outcome of various cancers including early stage NSCLCs but not LA-NSCLCs after iCRT. In this study, we investigated the impact of PNI on clinical outcome of iCRT followed by surgery in the patients with LA-NSCLCs. Methods: During 2009 to 2016, 70 patients underwent iCRT followed by surgery in Okayama University Hospital. We retrospectively calculated the PNI at (1) pre-iCRT, (2) pre-operation (Ope), and (3) post-Ope (about one month later) and reviewed the medical records. Results: The median age was 63 years old (range 34 – 78) and 53 patients were male. Forty-three patients were adenocarcinomas and 24 were squamous cell carcinomas. Clinical stages were IIA (n =3), IIB (n = 6), IIIA (n = 44), IIIB (n = 15), and IV (n = 2). Main regimen of iCRT was CDDP / DOC with concurrent radiotherapy (46 gray). Treatment responses were partial response (n = 44), no change (n = 24), and progressive disease (n = 2). Lung resections were lobectomy (n = 66), bi-lobectomy (n = 6), and pneumonectomy (n = 2) and additional procedure such as combined resection was performed in 43 patients (61%). Pathological responses were EF1 (n = 20), EF2 (n = 29), and EF3 (n = 2). The median values of PNI were significantly decreased during treatment course (50 (39 – 71) in pre-iCRT, 45 (31 – 58) in pre-Ope, and 41 (24 – 54)). We defined the cutoff value of PNI as 45 based on previous reports. The patients with high PNI (more than 45) in pre-iCRT showed significantly better prognosis than those with low PNI (3 years overall survival rate, 85% in high PNI vs 53% in low PNI, P < 0.03). Conclusion: Pre-treatment PNI and immunological statuses that were evaluated using PNI may affect clinical outcome of the patients who received the iCRT followed by surgery for LA-NSCLCs.

Keywords: nutrition, Prognostic Nutrition Index, non-small cell lung cancer, induction chemoradiotherapy

POSTER SESSION 2 – P2.02: LOCALLY ADVANCED NSCLC
PROGNOSTIC FACTORS
TUESDAY, DECEMBER 6, 2016

P2.02-053 DOES THE METHOD OF MEDIASTINAL STAGING CAUSE
THE MEDIASTINAL NODE CLEARANCE FOLLOWING TRIMODALITY THERAPY?
Jong Ho Cho, Hong Kwan Kim, Jheeok Kim, Jee Il Zo, Young Mog Shim, Yong Soo Choi
Department Thoracic & Cardiovascular Surgery, Sungkyunkwan University School of Medicine, Samsung Medical Center, Seoul/Korea, Republic of

Background: Outcomes of trimodality therapy for patients with persistent N2 have been well-known as grave. The aim of our study was to investigate whether the method of mediastinal staging could influence the mediastinal nodal clearance following trimodality therapy. Methods: We retrospectively reviewed medical records of 574 patients with clinical stage IIIA-N2 non-small cell lung cancer (NSCLC) who underwent surgery after neoadjuvant CRT from 1997 to 2013. Clinical outcomes were analyzed and compared in those who had EBUS (n = 147), Mediastinoscopy (n = 341), and others (n=86) after neoadjuvant CRT/CRT in a single institution. Results: The median number of dissected lymph node during the operation was 20 (range, 0-50) in EBUS, 14 (range, 1-52) in mediastinoscopy, and 18 (range, 4-40) in others (p=0.001). The median number of lymph node metastases was 2 (range, 0-23) in EBUS, 1 (range, 0-26) in mediastinoscopy, and 0 (range,0-14) in others (p=0.001). There were no differences of age, sex ratio, cell type, surgical extent, clinical T stage, and bulk N2 between these groups. The mediastinal nodal clearance rate (ypN0/1) after surgery was 36% (54/147) in EBUS, 58% (109/341) in mediastinoscopy, and 60.5% (52/86) in others (p=0.001). The ypN0 rate was 28.6% (62/147) in EBUS, 41.9% (143/341) in mediastinoscopy, and 51.2% (44/86) in others (p=0.001). Conclusion: We found that the mediastinal nodal clearance rate (ypN0/1) after surgery was higher in mediastinoscopy than in EBUS. The method of mediastinal staging could influence ypN0 stage following trimodality therapy.

Keywords: lung cancer, trimodality therapy, mediastinoscopy, EBUS

P2.02-055 PATHOLOGIC MEDIASTINAL NODAL AND
METABOLIC TUMOR RESPONSE TO PREDICT OVERALL SURVIVAL IN
STAGE IIA-N2 NSCLC AFTER NEOADJUVANT CHEMOTHERAPY
Christophe Dooms, Charlotte Van de Kerkoven, Paul De Leyn, Eric Verwaeren, Kann flirt, Sigrid Stroobants, Ingel Demedts, Sofie Derijcke, Bertil Decaluwe, Johan Vansteenkiste, Christophe Deroose
1University Hospitals KU Leuven, Leuven/Belgium, 2University Hospitals Leuven, Leuven/Belgium, 3Jessa Ziekenhuis, Hasselt/Belgium, 4University Hospital Antwerp, Edegem/Belgium, 5Kaz Delta Roesselare, Roesselare/Belgium, 6Azgroeninge, Kortrijk/Belgium

Background: Neoadjuvant chemotherapy (NCT) is a therapeutic option that is used in patients with resectable stage IIA-N2 NSCLC. We previously hypothesized that combined major histopathological mediastinal nodal response (≥10% residual tumor cells in nodal tissue) and metabolic FDG-PET response (≤50% SUVmax ≥60%) on the primary tumor could be regarded as a powerful surrogate of overall survival (OS) in stage IIA-N2 NSCLC given NCT and confirmed mediastinal nodal disease at diagnosis. This phase II prospective multicenter study aimed to validate the predictive power for OS of our restaging algorithm. Methods: Patients with resectable stage IIA-N2 NSCLC

Keywords: lung cancer, trimodality therapy, mediastinoscopy, EBUS
having mediastinal nodal disease proven by endosonography and primary tumor SUVmax at least 2.5 were eligible. All patients were scheduled for 3 cycles of NCT followed by video-assisted mediastinoscopy (VAM). A standardized PET/CT was performed at baseline, after one and three cycles. The primary endpoint was the predictive power for longer OS of a major histopathological mediastinal nodal response at VAM combined with a pre-defined primary tumor ≤SUVmax ≥60% at PET (good prognosis group) compared to all other situations (poor prognosis group). Under an assumption of a 2-year OS of 80% compared to 30% for the good versus poor prognosis group, respectively, 48 patients were required to have 80% power with 2-sided alpha of 0.05. Results: We enrolled 32 patients between 2009 and 2014. Two patients demonstrated stage IV at PET/CT after cycle one. All 3 cycles were given to 30 patients of whom 29 underwent VAM and 22 underwent surgical resection. Objective response rate (RECIST 1.1) was 64%. Complete pathological response occurred in 2 patients. Median OS was 26 months (all 2-year events occurred). In ITT, combined major histopathologic nodal and metabolic tumor response was associated with a trend towards longer OS (HR 0.29, 95%CI 0.14-1.09, P=0.07). Major histopathologic mediastinal nodal response was significantly associated with longer OS (HR 0.25, 95%CI 0.02-0.51, P=0.02), while metabolic ≤SUVmax ≥60% primary tumor response was only associated with a trend towards better OS (HR 0.41, 95%CI 0.17-1.27, P=0.14). Conclusion: Complete pathological response to NCT in stage IIIA-N2 NSCLC is infrequent and therefore not useful as a surrogate for OS. Combined major pathologic nodal and metabolic tumor response was associated with a trend towards longer OS. By contrast, a major histopathologic mediastinal nodal response with ≤10% residual tumor cells at VAM is well suited to be adopted as a surrogate of OS.

Keywords: Tumor response, Locally advanced NSCLC, SUVmax, neoadjuvant chemotherapy

POSTER SESSION 2 – P2.02: LOCALLY ADVANCED NSCLC PROGNOSTIC FACTORS
TUESDAY, DECEMBER 6, 2016

P2.02-056 FGFR GENE MUTATION IS AN INDEPENDENT PROGNOSTIC FACTOR IN SQUAMOUS NON-SMALL CELL LUNG CANCER, AND ASSOCIATED WITH LYMPH NODE METASTASIS
Li Jingjing1, Yan Shi1, Pan Yaqi1, Liu Zheng2, Qin Tan3, Yang Yue3, Woodward Emma1, Wu Nanc
1Laboratory of Genetics, Peking University Cancer Hospital & Institute, Beijing/China, 2Department of Thoracic Surgery II, Peking University Cancer Hospital & Institute, Beijing/China, 3Peking University Cancer Hospital & Institute, Beijing/China

Background: Targeting FGFRs is one of the most promising therapeutic strategies in squamous non-small cell lung cancer (SQCC). However, different FGFR genomic aberrations can be associated with distinct biological characteristics that result in different clinical outcomes or therapeutic consequences. Currently, the full spectrum of FGFR gene aberrations and their clinical significance in SQCC have not been comprehensively studied.

Methods: Next-generation sequencing was used to investigate FGFR gene mutations in 143 patients with SQCC who had not been treated with chemotherapy or radiotherapy prior to surgery. Results: FGFR gene mutations were identified in 24 cases, resulting in an overall frequency of 16.9%. Among the mutations, 7% (10/143) were somatic mutations, and 9.8% (14/143) were identified in 24 cases, resulting in an overall frequency of 16.9%. Among the mutations, 7% (10/143) were somatic mutations, and 9.8% (14/143) germline mutations. FGFR mutations were significantly associated with an increased risk of lymph node metastasis (adjusted OR = 4.75, 95% CI = 1.78-12.77, P = 0.002). SQCC patients with a FGFR somatic mutation had shorter OS (overall survival, log rank P = 0.008) and DFS (disease-free survival, log rank P = 0.006) compared with those without an FGFR mutation. The multivariate analysis confirmed that a somatic mutation was an independent poor prognostic factor for OS (HR: 2.76, 95% CI: 1.05-7.27, P = 0.04) and was associated with reduced DFS (HR: 2.22, 95% CI: 0.97-5.07, P = 0.06).

Conclusion: FGFR mutation may increase the risk of lymph node metastasis in patients with SQCC. FGFR somatic mutation could be a useful biomarker for predicting poor clinical outcome in SQCC.

Keywords: lymph node metastasis, prognostic markers, FGFR mutation, squamous lung cancer

POSTER SESSION 2 – P2.02: LOCALLY ADVANCED NSCLC RT Techniques – TUESDAY, DECEMBER 6, 2016

P2.02-057 THE IMPORTANCE OF ADAPTIVE RADIOTHERAPY IN THE RADICAL TREATMENT OF LOCALLY ADVANCED NON SMALL CELL LUNG CANCER
Slavica Maric1, Milomir Milakovic2, Aleksandar Kostovski1, Pavle Banovic1, Ljiljana Tadic-Latinić1
1Radiotherapy, International Medical Centers Banja Luka, Banja Luka/Bosnia And Herzegovina, 2Pathology, University Clinical Center, Banja Luka/Bosnia And Herzegovina

Background: Large radiation volumes and low radiation tolerance of surrounding organs of risk often limits the delivery of radical dose in the treatment of locally advanced non small cell lung cancer. Aim of this study is to quantify the differences between initial planning target volume and planning target volume on repeated simulation after 22-23 fractions, and consequent need for re-planning and adaptive radiotherapy. Methods: This study included 10 patients with diagnosis NSCLC, clinical stage IIIA and IIB, in which is indicated radical radiotherapy with or without chemotherapy in period May 2015 - December 2015. Seven patients were treated with 3D conformal radiotherapy technique, and three patients were treated with IMRT technique. All patients were compared by the values of planning target volume expressed in cm$^3$ and equivalent spherical diameter expressed in cm$^3$ initially, and on repeated simulation after 22-23 fractions. Evaluation and need for re-planning was done by the comparison both values. Results: Based
on the results t-test there was statistically significant difference (p<0.05) between values of planning target volume initially at the beginning of the treatment, and after 22-23 fraction. Also, based on the results t-test there was statistically significant difference (p<0.05) between values of equivalent spherical diameter initially and on repeated simulation during the course of radical radiotherapy. Conclusion: Adequate monitoring of clinical response and anatomical changes during course of radical radiotherapy with adequate re-simulation, re- contouring and re-planning give us possibility of reducing large radiation volumes with precise dose delivery to the planning target volume. With this concept we have possibility to improve local control and consequently minimize toxicity on organs of risk.

Keywords: radical radiotherapy, re-planning, NSCLC, planning target volume

POSTER SESSION 2 – P2.02: LOCALLY ADVANCED NSCLC
RT TECHNIQUES – TUESDAY, DECEMBER 6, 2016

P2.02-058 MODERATELY HYPOFRACTIONATED RADIOTHERAPY IN LOCALLY ADVANCED NON SMALL CELL LUNG CANCER: A SINGLE INSTITUTION RETROSPECTIVE ANALYSIS
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Background: Radiation dose escalation using hypofractionation might improve clinical outcomes. Aim of the study was to evaluate outcomes, safety and feasibility of a moderately hypofractionated Radiotherapy (Hypo-RT) regimen for pts with LA-NSCLC. Methods: Between 2008 and 2015 44 consecutive pts with LA-NSCLC were treated using a HYPO-RT regimen. Thirty-two pts were male,12 female. Mean age was 66.2 years. Primary tumor was adenocarcinoma in 16 pts, SCC in 27. Giant Cell neuroendocrine Carcinoma in 1 pt. Three pts had clinical stage IIA-IIIB, 19 pts IIIA and 21 IIIB. Chemotherapy was administered before Hypo-RT in 37 pts, 7 pts underwent exclusive RT. Mean total RT delivered to site of persistent disease was 61 Gy (range 45-66Gy) and mean total treatment time was 40 days in 5,7 weeks(range 3-8) Daily fraction ranged between 2.2 and 3 Gy. RT was temporarily interrupted in 1 pts due to acute toxicity. Results: After a median follow up of 13.7 months, 21 pts were alive, whereas 25 pts had died (18 pts due to disease progression and 7 from other causes). Complete response was achieved in 6 pts, partial response in 16 and stable disease in 10 with an overall response rate (ORR) equal to 72.7%. Twenty-one pts showed locoregional relapse; 17 pts distant metastasis and 6 pts both of them. Median overall survival (OS) was 61.7 months while 1-, 3- and 5-year OS were 68.9%(±7,2%SE), 44.9%(±8.3%SE) and 25.5(±10.5)SE), respectively. At univariate analysis local failure, stage and response to CHT-RT treatment showed a statistically significant impact on OS with better prognosis for pts in stage IIIA, achieving a complete response and not experiencing locoregional relapse (p < 0.04, < 0.05, < 0.02 respectively). At the same interval progression free survival was 52.3%(ES4.7),17.8%(ES6.6) and 11.9% (ES6.5) while 3- and 5-years locoregional control was 24.6%(ES4.5) and 11.7%(ES4.9). Acute toxicities were reported in 27 pts: 6 pts had G1-G2 skin dermatitis, 16 pts G1-G2 esophagitis and 4 pts G1-G2 pneumonitis. About late toxicities 7 pts experienced G1-G2 pneumonitis while 3 pts had G1-G2 esophagitis. No deaths related to the treatment were recorded. Conclusion: Hypo-RT proved to be a feasible and well tolerated treatment for pts with LA-NSCLC showing very promising results in terms of overall response rate and clinical outcomes. Further studies are needed to confirm these results and introduce HYPO-RT in the clinical routine

P2.02-059 NEW TREATMENT STRATEGY IN INOPERABLE LOCOREGIONALLY ADVANCED NSCLC: CARM CONE BEAM CT-GUIDED SELECTIVE INTRAARTERIAL CHEMOTHERAPY
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Background: The optimal treatment of patients with stage III Non-small cell lung cancer (NSCLC) has not been clearly defined. Although there are many treatment options, none of them have a high probility of cure. A multidisciplinary approach is important for this patients. Aim of this study was to determine efficacy and non-inferiority of Carm Cone Beam CT (CABCT)-guided selective intraarterial chemotherapy (IACH) for patients who had inoperable locoregionally advanced NSCLC. Methods: Patients: Our study included 27 Non-small cell lung cancer (NSCLC) patients who were treated with IACT in the Department of Medical Oncology at Antalya Memorial Cancer Center between September 2012 and March 2016. Only patients with inoperable NSCLC who had a life expectancy longer than 3 months were included in study. They were previously untreated patients. CHEMOTHERABILIZATION: The treatment was performed using intra-a-arterial platinum based combination chemotherapy every 21 days for 2-4 cycles by CABCT. In all patients, via the femoral artery, CABCT angiographies were taken and the feeding arteries of the tumors were identified. These arteries were then selectively catherized and cisplatin+docetaxel combination was infused. If patients had good response the treatment after first two cycles, they underwent the surgery. Other patients had continued chemoradiotherapy. Results: Two patients were female and twenty-five patients were male. Thirteen of patients had non-squamous, fourteen patients had squamous cell lung cancer. The average age of the patients was 58.9 years (range 46-78 years). The post-treatment radiological response evaluation of the patients as follows: 3 patients(11,1%) had stable disease, 19 patients(70,3%) had a partial response, 3 patients(11,1%) had a complete response and progressive disease was observed in 2 patients(7,4%). Objective Response Rate was 90.5%. Surgical resection was performed thirteen(46,1%) of the patients. A pathological complete response was achieved in 5 patients who were operated on after radiotherapy. Conclusion: This study has shown that our experience with IACH is an effective and less toxic in inoperable locoregionally advanced NSCLC regardless of the histology. This treatment strategy is combinations of surgery or chemoradiotherapy hopful for this patients.

Keywords: selective intraarterial chemotherapy, Carm Cone Beam CT, non-small cell lung cancer

POSTER SESSION 2 – P2.02: LOCALLY ADVANCED NSCLC
RT TECHNIQUES – TUESDAY, DECEMBER 6, 2016

P2.02-060 SBRT AND SEQUENTIAL CHEMOTHERAPY FOR STAGE IIA TO IIB NON-SMALL CELL LUNG CANCER – A PHASE I DOSE ESCALATION STUDY
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Background: Stereotactic Body Radiation Therapy (SBRT) has become an effective and less toxic in inoperable locoregionally advanced NSCLC. However, its role in larger tumors is undefined, and patients with inoperable locally advanced NSCLC are treated with conventionally fractionated radiation therapy and chemotherapy. Our phase I dose escalation trial evaluates the maximum tolerated dose (MTD) of SBRT in patients with stage IIA to IIB NSCLC involving a larger primary tumor and/or hilar involvement. Methods: Patients with inoperable stage IIA to IIB (T2b-N4M0 and TanyN1M0) NSCLC fit for SBRT and sequential chemotherapy were eligible. SBRT dose escalation levels with inoperable stage IIA to IIIA (T2b-T4N0M0 and TanyN1M0) NSCLC due to excellent local control and survival outcomes. Its role in larger tumors is undefined, and patients with inoperable locally advanced NSCLC are treated with conventionally fractionated radiation therapy and chemotherapy. Our phase I dose escalation trial evaluates the maximum tolerated dose (MTD) of SBRT in patients with stage IIA to IIB NSCLC. Results: Nine patients were enrolled, three at the 40 Gy and six at the 50 Gy dose level. All patients received SBRT to the prescribed dose. Two patients receiving 50 Gy were no longer eligible for chemotherapy after SBRT. Median follow-up time was 6.3 months (range: 2.5 - 28.9). At the 40 Gy dose level, there was one patient with late (≥3 months post-SBRT) grade 3 pneumonia and one with late grade 3 bronchial obstruction. The dose was escalated to 50 Gy. At the 50 Gy dose level, two patients experienced persistent grade 3 radiation pneumonitis. One patient also had acute grade 4 respiratory insufficiency and contralateral pulmonary edema. In the expanded 50 Gy cohort, one patient experienced persistent grade 3 nausea, vomiting, and abdominal toxicity.

Results: Patient characteristics included 1 male and 8 female patients, with a median age of 66 years (range: 51 - 77). Tumors were adenocarcinoma in 6 patients, squamous cell in 2, small cell in 1, and 2 of unknown histology. Eleven patients had stage IIA, one had stage IIB, and one had stage IIIA NSCLC. At the 50 Gy dose, one patient had persistent grade 3 radiation pneumonitis and one had grade 2 neutropenia. No grade 4 or higher toxicities were observed. Conclusion: The MTD of SBRT and sequential chemotherapy in patients with stage IIA to IIB NSCLC was determined to be 50 Gy.

Keywords: SBRT, sequential chemotherapy, phase I dose escalation study

POSTER SESSION 2 – P2.02: LOCALLY ADVANCED NSCLC
RT TECHNIQUES – TUESDAY, DECEMBER 6, 2016
pain, and another developed grade 3 chest wall pain. Therefore 50 Gy was determined to be the MT0. On PRO-CTCAE questionnaires patients most frequently reported fatigue (75%), dyspnea (50%), cough (38%), and pain (38%) as interfering “quite a bit” or “very much” with their daily activities. Conclusion: We determined that 50 Gy in five fractions followed by sequential chemotherapy is the MT0 for SBRT in patients with stage IIA to IIIA NSCLC. Long-term outcomes and larger trials will be needed to assess whether SBRT results in superior local control and survival compared to conventional chemoradiation. Made possible by the generous support of the Dalle-Peze Foundation.

Keywords: Locally advanced NSCLC, stereotactic body radiation therapy (SBRT)

POSTER SESSION 2 – P2.02: LOCALLY ADVANCED NSCLC Toxicities – TUESDAY, DECEMBER 6, 2016

P2.02-061 ROLE OF MMP-2-1306C/T IN ONSET OF HEMATOLOGICAL TOXICITY IN LUNG CANCER PATIENTS RECEIVING FIRST LINE PLATINUM BASED THERAPY
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Background: Lung cancer is the most common and lethal cancer worldwide. Totally, about 85% of lung cancer cases could be classified as Non-Small Cell Lung Cancer (NSCLC) and most are diagnosed at advanced stage. Matrix metalloproteinases are a family of zinc endopeptidases with protostotic activity against the extracellular matrix proteins playing a key role in the process of tumor growth/metastasis. Genetic variants in matrix metalloproteinase-2 (MMP-2) gene may influence the biological function of this enzyme changing his role in carcinogenesis, hematopoietic recovery from chemotherapy toxicity and cancer progression. This study has investigated the association of single nucleotide polymorphism (1306C/T) in the MMP-2 promoter sequence, and the link with a strong hematological toxicity in lung cancer patients receiving first-line, platinum-based chemotherapy. Methods: Forty-seven patients (36 men and 9 women) with IIA/IV NSCLC stage were enrolled; information about hematologic toxicity (thrombocytopenia, neutropenia, anemia), gastrointestinal toxicity (nausea/vomiting), and smoking habits were collected through the clinical charts. Genotyping was performed using direct DNA sequencing. Results: 25/47 patients (53%) had the genotype 9A/7 (7%) patients had CT genotype and 14/47 (30%) TT genotype. A grade 2 anemia associated to grade 2-3 thrombocytopenia and/or G2-3 neutropenia was observed in 12/22 CC patients compared with 10/25 patients (p<0.01), after platinum-based therapy, patients with genotype TT showed a better response to treatment as compared with those carrying CT or CC genotype. Besides, this study showed that heavy smokers had a higher allelic frequency CC and this could indicate a possible correlation between genetic polymorphism, smoking status, and clinical outcome. Conclusion: These preliminary findings suggest that MMP-2 promoter polymorphism could be correlated with therapeutic response, in particular, the patients with TT genotype seem more protected from the hematological toxicity due to chemotherapy.

Keywords: Lung cancer, polymorphism, MMP-2, hematological toxicity

POSTER SESSION 2 – P2.02: LOCALLY ADVANCED NSCLC Toxicities – TUESDAY, DECEMBER 6, 2016

P2.02-062 ALTERATIONS IN PULMONARY FUNCTION TESTS PREDICT THE DEVELOPMENT OF RADIATION-INDUCED PNEUMONITIS IN ADVANCED NSCLC
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Background: Chemo and radiation therapy are the standard of treatment in patients with locally advanced NSCLC. Radiation pneumonitis is a frequent complication and it is associated with symptoms that decrease the quality of life and might result in pulmonary fibrosis or death. Methods: Prospective study from June 2013 to July 2015, in patients treated with concurrent chemoradiation for NSCLC at the Instituto Nacional de Cancerología of Mexico. All patients had pulmonary assessment at baseline (prior to chemoradiation) and at 6 weeks, 3, 6 and 12 months end of chemoradiation. The pulmonary function tests (PFT) included: spirometry, plethysmography, osclomtry, diffusing capacity for CO2, molar mass of CO2, arterial gasometry, 6 minutes walk and fraction of exhaled NO (FENO). Radiation pneumonitis was evaluated by RT0G criteria and the CTCAE V.4.0. The study was approved by the ethics committee and was registered in clinicaltrials.gov (NCT01508507). Results: Overall 52 patients were included and 37 patients completed one-year follow-up. Severe pneumonitis developed in 1/37 (29%) and 1/37 (40%), according to the RTOG criteria and the CTCAE V.4.0, respectively. Factors associated with pneumonitis development included age and dose per fraction (>250cGy). We observed as well that patients who developed pneumonitis had more often central and lower tumors, and percentage of irradiated lung with 20Gy greater than 35% (PA V20>35%) and 5Gy over 65% (PA V5>65%), PFTs alterations prior to treatment that identified the development of severe pneumonitis included: a lower forced expiratory volume in one second after bronchodilator (FEV1, p=0.02), the ratio for the residual volume between total lung capacity (RV/FVA, p<0.02) and FENO (p<0.04). All PFTs showed changes at the end of chemoradiation, particularly between the third and sixth month of treatment, with a slight recovery at 12 months, without returning to basal values. Although patients who developed pneumonitis had a greater deterioration in the spirometry and plethysmography, changes in PFTs during the first 12 weeks not predicted the development of pneumonitis. Conclusion: Alterations in FEV1, RV/FVA and FENO, prior to concomitant chemoradiation predict the development of severe pneumonitis in NSCLC. This study suggests that all patients who receive chemoradiation to the lung must be assessed by PFTs in order to identify patients at high risk for radiation pneumonitis, and have a close follow-up with an early start (beginning of symptoms) of steroids to reduce long-term complications.

Keywords: Pulmonary function tests, NSCLC, chemoradiation

POSTER SESSION 2 – P2.03a: ADVANCED NSCLC & CHEMO-THERAPY/TARGETED THERAPY/IMMUNOTHERAPY Clinical Trials – TUESDAY, DECEMBER 6, 2016

P2.03A-001 A RANDOMIZED PHASE III CLINICAL TRIAL OF ANLOTINIB HYDROCHLORIDE IN PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC)
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Abstracts
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Background: Anlotinib hydrochloride, a novel multi-targeted tyrosine kinase inhibitor (TKI) was found to exhibit excellent inhibitory efficiency on a variety of receptor tyrosine kinases (RTK) involved in tumor progression, especially the vascular endothelial growth factor receptor (VEGFR), fibroblast growth factor receptor (FGF, platelet-derived growth factor receptor (PDGFR) and stem cell factor receptor (c-KIT). This ongoing trial aimed at evaluating the efficacy and safety of anlotinib hydrochloride comparing with placebo in advanced NSCLC patients who had received at least two previous chemotherapy and EGFR/ALK targeted therapy regimens.

Methods: This Phase III, randomized, double-blind, placebo-controlled study (NCT 02388919) is ongoing in 31 centers in China under the supervision of Independent Data Monitoring Committee (IDMC). Pathological stage IIIB/IV adult advanced NSCLC patients (Pts) who had failed with at least two previous chemotherapy and EGFR/ALK targeted therapy regimens were eligible. The status of EGFR and ALK genes should be clear in all enrolled pts. Pts with sensitive EGFR or ALK mutations must have received and appeared intolerance to perversious targeted therapies. Pts were randomized (2:1) to receive Anlotinib hydrochloride or placebo once daily (12 mg) from day 1 to 1 of a 21-day cycle until progression. Dose reduction to 8 or 10 mg/day could be applied when grade 3 or 4 treatment-related toxicities were observed. The minimal sample size was estimated to 450 patients. The primary endpoint is overall survival (OS) and secondary endpoints are progression-free survival (PFS), overall response rate (ORR), disease control rate (DCR) and quality of life (QOL). Quality of life was assessed via EORTC QLQ-C30, safety is determined using standard NCI-CTCAE v4.02, and responses are evaluated according to RECIST v1.1. Results: This study started in February 2015, up to early July 2016, a total of 420 pts have been enrolled (93.3% of 450 pts). Among enrolled pts, about 80% were diagnosed as adenocarcinoma, EGFR mutation or ALK rearrangement was found in 1/3 of the pts. The overall analyses will start after 300 OS events. Conclusion: Anti-angiogenes is the main mechanism of Anlotinib hydrochloride for preventing the tumor progression. Results of randomized, placebo-controlled Phase II trial (NCT01924195) has been reported in WCLC 2015, however, advantages in PFS (4.8 vs. 1.2 months) and OS (9.3 vs. 6.3 months) were observed in Anlotinib arm from the renewed data. Based on these exciting data, we are looking forward for the results of the Phase III trial.

Keywords: NSCLC, Anlotinib, multi-targeted tyrosine kinase inhibitor
P2.03A-004 SECOND-LINE THERAPY IMPROVES OVERALL SURVIVAL IN PRIMARY REFRACTORY NON-CELL LUNG CANCER (NSCLC) PATIENTS

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Background: The effect of palliative chemotherapy for non-small cell lung cancer (NSCLC) is well established. However, little is known on the efficacy of cytotoxic chemotherapy in patients whose tumors are refractory to first-line chemotherapy. We analyzed the outcome of all consecutive and unselected patients receiving palliative chemotherapy in a single institution to assess the efficacy of second-line chemotherapy in primary refractory NSCLC.

Methods: 462 consecutive patients with palliative treatment for NSCLC at the University Hospital Basel between 1990 and 2009 were analyzed. Measured outcomes were overall response rate (ORR), progression-free survival (PFS) and overall survival (OS). Patients with progressive disease (PD) as best response to first-line treatment were compared to patients with stable disease (SD), partial (PR) or complete remission (CR). Chi-square test was used for discrete, and Mann Whitney U tests for continuous variables, respectively. Probabilities of survival were calculated using the Kaplan-Meier estimator.

The log-rank test was used for comparing groups. Results: Median age was 63 years, 77% were male, 81% were smokers and 53% had adenocarcinoma. Median OS of the whole cohort was 11.3 months. 62.3% of patients were treated with a platinum-based (48.3% cisplatin-based) first-line therapy. Median PFS for first-line therapy was 3.0 months. 192 patients (41.6%) were primary refractory on first-line therapy. Median OS was significantly shorter for refractory patients compared to patients with CR, PR or SD (9.2 vs. 14.5 months, p<0.0001). Poorer initial performance status was significantly associated with primary refractory disease (p=0.015). All other baseline characteristics did not differ between refractory and responding patients. 67 (35%) primary refractory patients received a second-line therapy. The clinical benefit rate (CR+PR+SD) from second-line therapy was lower for primary refractory patients (2.2 vs. 4.6 months, p=0.26). Median OS was significantly longer for refractory patients receiving second-line chemotherapy vs. best supportive care (13.6 vs. 5.5 months, p=0.0001). Conclusion: More than 40% of patients are primary refractory to second-line chemotherapy vs. best supportive care (13.6 vs. 5.5 months, p=0.26). Median OS was significantly longer for refractory patients receiving second-line chemotherapy vs. best supportive care (13.6 vs. 5.5 months, p=0.0001). Poorer initial performance status was significantly associated with primary refractory disease (p=0.015). All other baseline characteristics did not differ between refractory and responding patients. 67 (35%) primary refractory patients received a second-line therapy. The clinical benefit rate (CR+PR+SD) from second-line therapy was lower for primary refractory patients (2.2 vs. 4.6 months, p=0.26). Median OS was significantly longer for refractory patients receiving second-line chemotherapy vs. best supportive care (13.6 vs. 5.5 months, p=0.0001).

Keywords: chemotherapy, second-line, primary refractory

P2.03A-005 A STUDY OF ENDOSTAR COMBINED WITH GEMCITABINE IN THE FIRST-LINE TREATMENT OF THE ELDERLY PATIENTS WITH ADVANCED NON-CELL LUNG CANCER

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Background: To observe the efficacy and safety of recombinant human endostatin (Endostar) combined with single-agent gemcitabine in the first-line treatment of the elderly patients with advanced non-small cell lung cancer (NSCLC). Methods: A total of 118 elderly patients with advanced NSCLC confirmed by pathology in Fuzhou Pulmonary Hospital of Fujian from Oct., 2007 to Sep., 2012 were randomly divided into treatment group and control group. Treatment group (n=62) was given the regimen of Endostar combined with single-agent gemcitabine, while control group only received the regimen of single-agent gemcitabine. After two cycles of chemotherapy, the efficacy was evaluated according to RECIST, and median time to tumor progression, median survival and 1-year survival rate in two groups were recorded. Besides, adverse reactions were evaluated every cycle based on NCICCT (version 3.0).

Results: Sixty-two patients in treatment group and 56 patients in control group completed more than two cycles of Endostar combined with gemcitabine. There were 11 cases with partial remission (PR), 36 with stable disease (SD)and 15 with progressive disease (PD). There was no statistical significance between two groups by comparison to the overall response rate (ORR) (17.7% vs. 10.7%, P=0.278), but significant differences were presented by comparison to the disease control rate (DCR) (75.8% vs. 57.9%, P=0.031) and median progression-free survival (mPFS) (4.0 months vs. 3.7 months, P=0.027). Compared with the median overall survival (mOS), there was no statistical significance(9.1 months vs. 8.5 months, P=0.418). The incidence of myelosuppression among adverse reactions was higher, main in phase G1 and G2. In the aspect of hematotoxicity, non-hematotoxicity and biochemical indexes, there was also no statistical significance between two groups (P>0.05). Conclusion: Endostar combined with single-agent gemcitabine has certain anti-tumor activity, better DCR and higher safety as well as clinical benefit rate for elderly patients with advanced NSCLC, which may be a promising regimen for the elderly patients with advanced NSCLC.

Keywords: Endostar, elderly, NSCLC, Recombinant human endostatin

P2.03A-006 FREQUENCY OF 2 YEAR PFS MILESTONE IN STAGE IV NSCLC PATIENTS TREATED WITH FIRST LINE PEMETREXED/ PLATINUM AND PEMETREXED MAINTENANCE

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Background: Focusing on median progression free and overall survival does not fully inform us, or our patients, of the maximum achievable benefit found at the tail end of the survival curve (Hellman M, JAMA Oncology 2016). Milestone metrics in this context may be more informative; however, mature data are scarce. Our anecdotal observations suggested that some of our non-squamous NSCLC pts treated with pemetrexed continuation maintenance had long-term disease control beyond the reported median PFS. The objective of our single institution retrospective study was to determine the % of patients who reach the 2 year PFS milestone in patients whose treatment plan included continuation pemetrexed maintenance. Evaluation of the potential predictive value of clinical parameters was a secondary objective. Methods: Pts with stage IV NSCLC who received at least once cycle of pemetrexed/platinum with planned pemetrexed maintenance (N = 241) between May 2010 and December, 2013 were included in this retrospective analysis. Minimum follow up for every patient was ≥ 24 months. Patient demographics, routine laboratory values, first and last dates of pemetrexed therapy, and date of progression were assessed using a Mann-Whitney-Wilcoxon test. Results: Median age 66, male/female 40/59, 75.7% 21% never smoker. The median progression free survival was 6.2 months. 34 pts (14.1%) had no progression of disease at ≥ 24 months since starting treatment with pemetrexed/platinum followed by pemetrexed maintenance. A PFS ≥24 months was associated with a lower baseline neutrophil/lymphocyte ratio (NLR) (median 3.3 vs 4.55; 25.75 percentile 3.23-3.96 vs 2.8-7.89; P=0.001). PS at baseline was also significantly associated with a PFS ≥24 months (p=0.02). Long term PFS was not significantly related to gender, age, sites of metastases, or number of disease sites. Conclusion: Considering that the two year OS rate for first line chemotherapy in clinical trials is approximately 25%, the 2 year PFS milestone rate of 14.1% patients is encouraging. Significantly lower baseline NLR, was observed in patients who reached the two year PFS milestone. Studies evaluating the potential predictive value of other clinical and molecular parameters are ongoing.
Background: To evaluate the efficacy and safety of pemetrexed, carboplatin and bevacizumab (PCB) followed by maintenance pemetrexed and bevacizumab (PM/BEV) in patients with metastatic NSCLC (mNSCLC) who have progressed on prior chemotherapy regimens. 

Methods: Patients with mNSCLC progressing on prior chemotherapy were eligible to receive PCB (carboplatin (AUC = 5.0) and pemetrexed (500 mg/m2)) followed by PM/BEV (pemetrexed (500 mg/m2) and bevacizumab (15 mg/kg)) every 4 weeks. The primary endpoints were overall survival (OS) and progression-free survival (PFS). Secondary endpoints included clinical response, reductions in tumour size, patient-reported outcomes, and safety. 

Results: From August 2011 to December 2013, 135 patients were enrolled in 26 centres in 14 countries (Australia, Brazil, Colombia, Italy, Mexico, Spain, Thailand, Turkey, USA and Venezuela). At the data cutoff date, 129 patients were assessable for safety and 116 for efficacy. Median age was 66 years (range 23–87) and 51% were female. The most common histology was adenocarcinoma (60%). The median number of prior chemotherapy regimens was 3 (range 1–7). The median number of prior RECIST responses was 1 (range 0–4). The median OS and PFS were 9.4 months (95% CI 7.6–11.3) and 5.6 months (95% CI 4.7–6.7), respectively. The clinical responses were 32% and 21% (95% CI 21%–32%) for objective response and clinical benefit rate, respectively. When adequately assessed, 63% of patients experienced reductions in tumour size. Grades 3 and 4 adverse events were common (80% and 19%, respectively), with the most frequent being anaemia (24%), neutropenia (19%), and thrombocytopenia (19%). 

Conclusion: PCB followed by PM/BEV was well tolerated and demonstrated clinical activity in patients with mNSCLC who had progressed on prior chemotherapy.
Background: Lung cancer is the number one cause of cancer-related death. 80% of patients present with advanced disease, and first line standard of care is multi-agent chemotherapy; however, overall 2-year survival is only 15%. Metformin, a well-tolerated oral biguanide used in diabetes, is thought to have anti-cancer effects via a variety of proposed mechanisms. Methods: This is a single-arm study with a randomized control arm for reference to expected 1-year progression-free survival (PFS), the primary endpoint, defined as the proportion of patients alive without disease progression at 1 year of treatment. Non-diabetic, chemotherapy-naive patients with advanced non-squamous NSCLC were randomized 3:1 to Arm A:Arm B. (NCT01578551) Arm A consisted of standard doses of paclitaxel, carboplatin, bevacizumab (B) until disease progression. Arm B consisted of standard doses of PCB x 4-6 cycles, followed by B until disease progression. Results: The 95% CI lower bound exceeded 15%, the proportion of patients alive without disease progression at 1 year of 1-year progression-free survival (PFS), the primary endpoint, defined as the range: 37-64) in Arm A and 64 years (range: 55-70) in Arm B. One-year PFS for patients and 33% of Arm B patients were male. Median age was 58 years.

Conclusion: Paradoxically worse OS and PFS in patients with high plasma levels of pemetrexed and its metabolites could not improve overall survival (PFS/OS). However, sampling times in population pharmacokinetic (PK) analyses of pemetrexed are limited. We performed population PK modeling of pemetrexed during the treatment period and evaluated total systemic exposure as a predictor. Methods: In a prospective observational multi-center study, treatment-naive patients with stage IIB or IV NSCLC receiving pemetrexed/platinum treatment were enrolled. Pemetrexed, dosed based on body surface area (500mg/m²), was administered as a 10-minute intravenous infusion every 21 days. Prior to and weekly after each pemetrexed administration, plasma sampling was performed (cycle-PK). Simultaneously, glomerular filtration rate (GFR) was estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula. In a subgroup, blood samples were collected at 10, 30 minutes and 1, 2, 6, 8, 24 hours after start of pemetrexed infusion (24-hour-PK). We used a recently validated assay to quantify plasma pemetrexed concentrations (Stoop et al, J Pharm Biomed Anal 2016;128:1-8). Population PK analyses were performed using nonlinear mixed effects modeling (NONMEM version 7.2). The final model, based on both cycle-PK and 24-hour-PK, was used to estimate the area under the plasma concentration versus time curve during cycle 1 (AUC cycle). With a Cox-regression analysis we examined the relation between AUC cycle and OS/PFS, adjusted for known prognostic factors (sex, disease stage, WHO performance-score). Results: For 97 of the 151 patients, concentrations of pemetrexed were quantified (24-hour-PK, n=15; cycle-PK, n=82). A two-compartment model parametrized (population estimate (%standard error of the estimate) in terms of clearance (CL, 5.44L/h [4.9%), central distribution volume (V1, 19.6L [11.3%]), peripheral distribution volume (V2, 173L [32.7%]), intercompartmental clearance (Q; 0.19L/h [31.6%]) and incorporated between-patient variability of CL (10.7%), and Q (24%). Results from the final model showed that GFR and other covariates did not improve the estimation of the parameters. The AUC cycle was significantly different between males (190.8;64.9 mg·h/L) and females (165.4;47.2 mg·h/L). When we stratified for sex, the highest quartile of AUC independently predicted worse OS (HR=3.06, 95%CI: 1.43-6.57) and PFS (HR=2.79, 95%CI: 1.36-5.70), adjusted for the remaining prognostic factors. GFR and other covariates did not improve the estimation of the parameters. The AUC cycle was significantly different between males (190.8;64.9 mg·h/L) and females (165.4;47.2 mg·h/L). 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(PEMCIS; PEM 500mg/m² and CIS 75mg/m²) or PEM-carboplatin (PEMCAR; CAR AUC=5). Patients with at least disease stabilization after four cycles and a favorable toxicity profile were eligible for PEM maintenance therapy. Prior to the initial PEM/platinum baseline, serum creatinine (μmol/l) was obtained. Subsequently, prior to and weekly after each administration of PEM/platinum serum creatinine was measured. Glomerular filtration rate (GFR) was estimated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula. Acute kidney disease (AKD) was defined as 1.5-fold increase of serum creatinine and/or decrease in GFR 35% or GFR<60ml/min within 3 months (KDIGO). Results: Of the 151 patients starting PEM-based therapy, the majority of patients had stage IV disease (86.8%) and they were treated with PEMCIS (64.2%) or PEMCAR (35.8%). During the first four cycles, treatment was discontinued in four patients (2.6%) due to AKD. Patients starting maintenance therapy (n=44; 29.1%) received a median number of 4 PEM cycles. During maintenance treatment with PEM, 12 patients developed AKD (27.3%); three patients could continue treatment after recovery of renal function and in one patient AKD was a part of septic shock. The remaining eight patients (18.2%) stopped treatment due to renal impairment. From patients with a decreased renal function at baseline (eGFR<90ml/min) a significantly higher proportion of patients stopped maintenance therapy due to renal impairment compared to patients with an eGFR≥90ml/min at baseline (6/11 vs. 2/33, p<0.05). Conclusion: Patients have a significant risk of developing nephrotoxicity leading to treatment discontinuation during maintenance therapy, especially if the renal clearance is impaired at the start of induction PEM/platinum therapy. In those patients a cumulative systemic dose of PEM or increased susceptibility may play a role in the development of nephrotoxicity. Patients might benefit from altered renal protective strategies, like continuation of hydration during maintenance therapy or dose-adjustment based on renal function. This study was funded by ZonMw, the Netherlands.

Keywords: maintenance therapy, advanced NSCLC, nephrotoxicity, pemetrexed

POSTER SESSION – P2.03A: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/ IMMUNOTHERAPY CLINICAL TRIALS – TUESDAY, DECEMBER 6, 2016

P2.03A-013 CHEMOTHERAPY IS BENEFICIAL FOR OCTOGONARIANS WITH NON-SMALL CELL LUNG CANCER (NSCLC)
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Background: In Sweden, almost half of the patients diagnosed with lung cancer diagnosis are more than 70 years old and indeed 14% were 80 years and older. Treatment of the elderly with lung cancer has, therefore, become an important issue. In the Stockholm county, almost all patients with lung cancer are referred to Karolinska University Hospital. We performed a retrospective study of our patients to demonstrate how octogenarians with non-small cell lung cancer (NSCLC) treated with chemotherapy responded in real-life clinical practice Methods: A retrospective observational study of all elderly (>80 years) patients with NSCLC referred to Department of Respiratory Medicine, Karolinska University Hospital, Stockholm until June, 2016 Results: In total, 2350 patients were newly diagnosed with lung cancer during this period. 453 (19.2%) were 80 years or older and had luminal treatment. The short follow-up duration may limit interpretation of Part 2 efficacy. The Part 2 safety profile was consistent with Part 1 (data to be presented).

Table. The Most Common Treatment-Emergent Adverse Events in Part 1

<table>
<thead>
<tr>
<th>Event, n (%)</th>
<th>All-Grade</th>
<th>Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>9(60)</td>
<td>5(33)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>9(60)</td>
<td>1(7)</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>2(13)</td>
<td>2(13)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>2(13)</td>
<td>2(13)</td>
</tr>
</tbody>
</table>

*Common all-grade (≥30%) or grade 3/4 (≥10%) events. Conclusion: Ruxolitinib 15 mg BID had an acceptable safety profile in combination with pemetrexed/cisplatin as first-line treatment of patients with stage IIIB/IV or recurrent nonsquamous NSCLC.

Keywords: non-small cell lung cancer, keyword, Ruxolitinib

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POSTER SESSION – P2.03A: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/ IMMUNOTHERAPY CLINICAL TRIALS – TUESDAY, DECEMBER 6, 2016

P2.03A-014 A DOSE-FINDING AND PHASE 2 STUDY OF RUXOLITINIB PLUS PEMETREXED/CISPLATIN FOR NONSQUAMOUS NON-SMALL CELL LUNG CANCER (NSCLC)
Giuseppe Giaccone1, Rachel Sanborn2, Salina Waaqar3, Alex Martinez3, Santiago Ponce2, Huiling Zhen2, Gerard Kennealey3, Susan Erickson-Viitanen4, Eric Schaefer4
1Medical Oncology, Georgetown University, Washington/D/United States of America, 2Earle A. Chiles Research Institute, Providence Cancer Center, Portland/ OR/United States of America, 3Washington University, St. Louis/MO/United States of America, 4Vall D’Hebron University Hospital, Barcelona/Spain, 512 de Octubre University Hospital, Barcelona/Spain, 6Incyte Corporation, Wilmington/DE/United States of America, 7Highlands Oncology Group, Fayetteville/AR/United States of America

Background: Dysregulation of the JAK/STAT pathway contributes to abnormal inflammatory responses, oncogenesis, treatment resistance, and poor prognosis in NSCLC. This phase 2 clinical trial evaluated the JAK/ JAK2 inhibitor ruxolitinib+pemetrexed/cisplatin as first-line treatment for patients with stage IIIB/IV or recurrent nonsquamous NSCLC and systemic inflammation (per modified Glasgow Prognostic Score [mGPS]). Methods: Key inclusion criteria were mGPS of 1/2 and ECOG performance status c3. Part 1, an open-label, 21-day safety run-in, assessed ruxolitinib (15 mg BID [chosen dose for Part 2]) plus pemetrexed (500 mg/m² IV on Day 1) and cisplatin (75 mg/m² IV on Day 1). Ruxolitinib dose selection for Part 2 required c3 dose-limiting toxicities (DLTs) for 9 evaluable patients. Part 2 randomized patients to ruxolitinib+pemetrexed/cisplatin or placebo+pemetrexed/cisplatin. The trial was terminated early for lack of efficacy in other solid tumor programs in patients with high systemic inflammation. Results: All 15 patients enrolled in Part 1 received ruxolitinib 15 mg BID plus pemetrexed/cisplatin. Median age was 64 years; male, 80%; mGPS 1, 80%. Median treatment duration was 140 days. The Table reports Part 1 safety data. Four patients were ineligible for DLTs (<80% compliance, n=2; disease progression, n=2). No DLTs occurred in 11 evaluable patients. The Part 1 overall response rate (ORR) was 53% (8/15; all partial responses). At study termination, 39 and 37 patients were randomized in Part 2 to ruxolitinib and placebo, respectively. Median treatment duration was 43 days. ORR was 31% (12/39) with ruxolitinib+pemetrexed/cisplatin versus 35% (13/37) with placebo+pemetrexed/cisplatin (all partial responses). The short follow-up duration may limit interpretation of Part 2 efficacy. The Part 2 safety profile was consistent with Part 1 (data to be presented).

Table. The Most Common Treatment-Emergent Adverse Events in Part 1

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<thead>
<tr>
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<th>All-Grade</th>
<th>Grade 3/4</th>
</tr>
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<tbody>
<tr>
<td>Anemia</td>
<td>13(87)</td>
<td>5(33)</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>11(73)</td>
<td>2(13)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>10(67)</td>
<td>1(7)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>9(60)</td>
<td>3(20)</td>
</tr>
<tr>
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<td>5(33)</td>
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*Common all-grade (≥30%) or grade 3/4 (≥10%) events. Conclusion: Ruxolitinib 15 mg BID had an acceptable safety profile in combination with pemetrexed/cisplatin as first-line treatment of patients with stage IIIB/IV or recurrent nonsquamous NSCLC.

Keywords: non-small cell lung cancer, keyword, Ruxolitinib

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Journal of Thoracic Oncology • Volume 12 Issue S1 January 2017
Background: Advanced cancer patients with elevated systemic inflammatory markers have significantly poorer chemotherapy response and shorter overall survival compared to patients without inflammation. However, mechanisms underlying this association are unclear. There is an urgent need to identify these mechanisms as a high proportion of advanced cancer patients present with systemic inflammation (-25%). This study aimed to determine the impact of inflammation status, as determined by the neutrophil-to-lymphocyte ratio (NLR), on drug pharmacokinetics and clinical outcomes, including patient toxicity, chemotherapy cycles received, response and survival, in patients with advanced non-small cell lung cancer (NSCLC). Methods: Seventy-two advanced NSCLC patients were recruited for a planned 6 cycles of carboplatin (target AUC 6 mg/mL/min) and paclitaxel (175mg/m2) chemotherapy. Drug concentrations from the first chemotherapy cycle were measured and analysed using population pharmacokinetic modelling. Clinical data and pharmacodynamic endpoints were also collected. Univariate analysis and multivariable regression analysis were used to identify relationships between NLR status (NLR ≤5 and NLR > 5) to pharmacokinetic parameters and clinical outcomes. Results: Patient demographics were not different between low and high NLR groups except for nutritional status. Patients with NLR > 5 had increased carboplatin exposure but no associations were found with paclitaxel pharmacokinetics. Increased carboplatin exposure associated with increased toxicities. Patients with elevated inflammation had serious clinical consequences including dose-limiting toxicities leading to reduced cycles of first-line chemotherapy, poor response and shorter overall survival. Conclusion: Advanced NSCLC patients with elevated inflammation have alterations in drug pharmacokinetics that may be negatively impacting their clinical outcomes. This under-appreciated inflammatory-mediated change in pharmacokinetics is a potential source of inter-individual variability that may be reduced by dose individualisation according to inflammatory status. Future trials of this approach need to be investigated to assess the impact on survival of advanced cancer populations treated with platinum-based chemotherapy.

Keywords: biostatistics, pharmacokinetics, Biomarkers, inflammation.
experienced after chemotherapy start, exposed patients to a higher risk of anticipatory CINV and of acute/delayed CINV respectively, as confirmed by the multivariate logistic model at T0 and by GEE overtime. Conclusion: Even if clinical staff was revealed to be aware and sensitive about patients' status and perceptions, CINV still represents a problem among patients undergoing chemotherapy, with this study further confirming that particular attention should be given to anxiety due to its key role in CINV development.

Keywords: chemotherapy-induced nausea and vomiting, first-line treatment, lung cancer

POSTER SESSION 2 – P2.03A: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/IMMUNOTHERAPY

CLINICAL TRIALS – TUESDAY, DECEMBER 6, 2016

P2.03A-018 A PHASE I/II STUDY OF ALISERTIB, AN ORAL AURORA KINASE INHIBITOR, IN COMBINATION WITH ERLOTINIB IN PATIENTS WITH RECURRENT OR METASTATIC NSCLC

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Medical Oncology, Fox Chase Cancer Center, Philadelphia/PA/United States of America

Background: Erlotinib (E) is an oral reversible tyrosine kinase inhibitor targeting the epidermal growth factor receptor (EGFR), known to have efficacy in NSCLC. The aurora kinases are necessary for cell cycle regulation and may have altered function in certain cancers; alisertib (A) is an oral selective aurora kinase A inhibitor. Preclinical data suggested that the combination of an EGFR inhibitor and aurora kinase inhibitor may have synergistic effects in wild-type EGFR NSCLC patients, leading to this phase I/II trial. Methods: Using a 3+3 dose escalation design, A was increased over four dose levels from 30 mg - 50 mg twice daily. E was given daily at 100 mg in D1 and 150 mg in D2-4. A was given on days 1-7 of a 21 day cycle along with daily E. Key eligibility criteria: age > 18, histologically confirmed NSCLC, ECOG PS 0-1, prior appropriate first line therapy, acceptable organ function. Key exclusion criteria: EGFR mutation, prior treatment with an EGFR pathway inhibitor or aurora kinase inhibitor. Results: We report our experience with the phase I portion of this study and plans for the phase II portion. Eighteen patients were treated on four dose levels. Patient characteristics: Median age 61, M/F (8/10), 10/18 had received RT in addition to systemic therapy. 14/18 patients completed at least 2 cycles. Median number of cycles completed was 6. Common drug-related AEs of any grade were fatigue (89%), anemia (83%), leukopenia (78%), dyspnea (78%), diarrhea and anorexia (61% respectively). Drug-related Grade 3/4 AE included neutropenia and leukopenia (33%) each, febrile neutropenia, lymphopenia and anemia (11% each). Two DLT occurred at DLA (febrile neutropenia, neutropenia delaying a cycle by 7 days, both in cycle 1). Disease responses were noted, including one patient with a PR who completed 10 cycles, and 5 patients who achieved SD. Conclusion: In patients with recurrent/metastatic NSCLC, the combination of A and E was tolerable. However, the maximum administered dose (E 150 mg daily + E 50 mg BID) led to two DLT, thus the MTD was declared at D3 (E 150 mg + A 40 mg BID); anti-tumor activity was noted. Updated preclinical data from Kras mutated and WT cell lines indicate activity of this combination in KRAS mutated whereas drug alone is ineffective. Based on this data, a protocol amendment was submitted to allow only patients with KRAS mutations to be treated in the phase II portion of the study.

Keywords: alisertib, KRAS, NSCLC, Erlotinib

POSTER SESSION 2 – P2.03A: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/IMMUNOTHERAPY

CLINICAL TRIALS – TUESDAY, DECEMBER 6, 2016

P2.03A-019 A RETROSPECTIVE ANALYSIS OF NANOPARTICLE ALBUMIN BOUND PACLITAXEL IN CHINESE PATIENTS WITH RECURRENT ADVANCED NON- Small CELL LUNG CANCER IN A SINGLE CENTER

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1Department of Medical Oncology, Cancer Institute and Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing/China, 2School of Public Health, Capital Medical University, Beijing, Beijing/China

Background: This is the first report describing the safety and short-term efficacy of nanoparticle albumin bound paclitaxel (Nab-PTX) as monotherapy administered weekly in the treatment of Chinese patients with recurrent advanced non-small cell lung cancer (NSCLC), and analyzing potential factors that may affect prognosis. Methods: Patients with recurrent advanced NSCLC who received an weekly nab-paclitaxel regimen (130 mg/m²/week) treatment were eligible. Toxicity and response according to the RECIST criteria were summarized in the study. Classification and regression tree (CART) analysis was performed to estimate the effect of variables (age, gender, performance score, smoking, clinical stage, pathological type, previous line of therapy, treatment cycles, EGFR status, EGFR/ALK/Tki, SPARC expression) on PFS. The Kaplan–Meier analysis was used to estimate the effect of terminal tree notes. Results: A total of 104 patients were included in the study from June 2010 to March 2014 in the Department of Medical Oncology, Cancer Hospital, Chinese Academy of Medical Sciences,. The median follow-up period was 9.56 months (0.92–34.00 months). The overall response rate was 21.4%, and the disease control rate was 73.8%. The median PFS was 4.53 months (95% CI: 3.518–5.542), and the median OS was 12.53 months (95% CI: 10.502–14.558). Grade 3 adverse events were neutropenia (8.8%), peripheral neuropathy (4.8%), myalgia/arthritis (4.0%), and fatigue (1.9%), respectively. Grade 4 toxicities rarely occurred except neutropenia (1.0%). CART analysis identified 4 terminal nodes based on therapy cycles, age and therapy line. In the four subsets, those with > 4 therapy cycles had the lowest PFS (Median: 1.80 months). Those with < 4 cycles and age ≥70 years had the longest PFS (Median: 8.83 months). The median PFS was significantly different between the four subgroups (P<0.000). In addition, PFS in the > 4 therapy cycles group was better than the without group (Median: 6.23 vs. 1.80 months, P<0.000). No PFS significant differences were observed for both age (≥70 years vs <70 years; Median: 8.83vs 5.87 months, P=0.06) and lines of therapy (> third-line vs < third-line; Median: 6.37 vs 4.60, P=0.063). A trend of a benefit in PFS in favor of > 70 years age and > third-line groups was found in our treatment. Conclusion: The weekly Nab-PTX regimen was effective and well-tolerated in patients with recurrent advanced NSCLC. Treatment cycles factors may be used to predict the therapeutic efficacy of Nab-PTX. Nab-PTX was also found the favourable survival benefit in older population (aged ≥70 years) and patients with > third-line therapy.

Keywords: nanoparticle albumin bound paclitaxel (Nab-PTX), advanced non-small cell lung cancer, chemotherapy

POSTER SESSION 2 – P2.03A: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/IMMUNOTHERAPY

CLINICAL TRIALS – TUESDAY, DECEMBER 6, 2016

P2.03A-020 METRONOMIC ORAL VINORELBINE MONOTHERAPY IN ELDERLY PATIENTS WITH ADVANCED NSCLC

Kostas Tzimopoulos, Ermis Tsaroucha, Erini Bourgani, Charalabos Kerasiotis, Anastasios Kalianos, Christina Kolokytha, Angeliki Rapti

2nd Pulmonary, Hospital of Chest Diseases of Athens, Athens/Greece

Background: Metronomic chemotherapy involves chronic administration of low-dose chemotherapy at regular short intervals, with the aim to induce prolonged cancer control without significant side effects. Aim: to evaluate metronomic oral vinorelbine in elderly patients with advanced NSCLC. Methods: Chemotherapy naive patients with a mean age of 72.8 yrs with NSCLC stage IIIb-IV and PS 0-2 were enrolled in this trial. Vinorelbine was administered orally at a dose of 40mg three times a week, until disease progression or unacceptable toxicities occurred. Results: Thirty-four patients were enrolled (19 adenoca 7 squamous 1 NSCLC). Thirty were eligible for evaluation.10 pts 33.3% had PS 2 and 7 (23.3%) had comorbidities (COPD and/or Heart failure). A partial response was observed in 6 patients (20%) and 12 (40%) had stable disease. After a median follow up period of 24.2 months, the median progression-free survival period (PFS) was 7.00 months (95%CI 4.9–9.1 months). No significant difference was found in PFS between patients with adenoca and squamous (5.00 vs 6.39 months p=0.05) Four patients (13.3%) showed a clinical improvement changing their PS from 2 to 1. Most adverse events were grade 1-2 peripheral neuropathy, dysgeusia and nephrototoxicity and there was no need for dose reduction or discontinuation of vinorelbine. Conclusion: Considering the PFS period and the negligible toxicity metronomic oral vinorelbine seems to be a useful and safe therapeutic option for elderly patients with advanced NSCLC.

Keywords: metronomic, vinorelbine, NSCLC

POSTER SESSION 2 – P2.03A: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/IMMUNOTHERAPY

CLINICAL TRIALS – TUESDAY, DECEMBER 6, 2016

P2.03A-021 VINORELBINE/CARBOPLATIN VS GEMCITABINE/CARBOPlatin IN ADVANCED squamous CELL LUNG CANCER

Assaf Dayyoub1, Ali Hasan2, Ali Mohammed3

1Damascus University, Damascus/Syria, 2Medical Oncology, Damascus University, Damascus/Syria

Background: Assef Dayyoub, Ali Hasan, Ali Mohammed

POSTER SESSION 2 – P2.03A: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/IMMUNOTHERAPY

CLINICAL TRIALS – TUESDAY, DECEMBER 6, 2016
Background: Scc accounts for about 30-40% of lung cancer cases, and the majority presents with locally advanced or metastatic disease. Vinorelbine/carboplatin (VC) and gemcitabine/carboplatin (GC) are both third-generation combinations used in the treatment of NSCLC. VC and GC were similar with respect to efficacy, health-related quality of life (HRQOL) and toxicity in stage IIIB/IV NSCLC patients. The aim is to compare VC and GC with respect to efficacy, DFS, hematologic toxicity in stage IIIB/IV Scc lung cancer patients. Methods: Chemonaive patients with SCC lung cancer stage IIIB/IV and WHO performance status 0–2 were eligible. No upper age limit was defined. Patients received vinorelbine 25 mg/m² or gemcitabine 1000 mg/m² on days 1 and 8 and carboplatin AUC 4 on day 1 and six courses with 3-week cycles. During 13 months, 103 patients were included (VC, n=53; GC, n=50). Results: median DFS was 22 vs 24.5 weeks (p=0.42); ORR (3cycle) 49.5% vs 58% and ORR(6cycle) % 16.9% vs 16% in the VC and GC arm, respectively (p=0.48). nausea/vomiting showed no significant differences. More grade 3–4 anemia (P=0.009), thrombocytopenia (P=0.004) in the VC arm. There was more grade 3–4 leucopenia (P=0.28) in the VC arm, but the rate of neutropenic infections was the same (P=0.87). Conclusion: VC and GC are similar in treating advanced SCC lung cancer when regarding ORR and DFS, while grade 3–4 toxicity requiring interventions were less frequent when VC is compared to GC in advanced squamous cell lung cancer.

Keywords: GC, VC, First Line, Advanced squamous lung cancer

P2.03A-022 QOL AND FEBRILE NEUTROPENIA: JAPANESE PHASE 2 TRIAL OF DOCETAXEL WITH/OUT ANTI INFLAMMATORY AGENT IN 2ND LINE NSCLC

Yukie Omori1, Alan Brnabic2, Narayan Rajan1, Jianghui Park2, Setaro Enatsu3, Akira Inoue1
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Background: Febrile neutropenia (FN) is one of the serious complications associated with cancer chemotherapy and often leads to dose reduction and change of administration schedule which may affect treatment outcomes. This post hoc analysis explored the association between FN and patient reported outcomes (PRO). Methods: PROs were collected in the trial JCWS with Lung Cancer Symptom Scale (LCSS) and EQ-5D-3L. LCSS includes 6 symptom questions (loss of appetite, fatigue, cough, dyspnea, hemoptysis, pain) and 3 global QOL items (symptom distress, difficulties with daily activities, QOL) measured on a 0-100 mm scale, with higher scores representing greater symptom burden. PROs were collected at baseline (BL, during 14days till randomization), around Day 21 in every cycle, at the timing of discontinuation of treatment (randomization), around Day 21 in every cycle, at the timing of discontinuation (randomization), around Day 21 in every cycle, at the timing of discontinuation (randomization), around Day 21 in every cycle, at the timing of discontinuation (randomization), around Day 21 in every cycle, at the timing of discontinuation (randomization), around Day 21 in every cycle, at the timing of discontinuation (randomization). Compliance with LCSS and EQ-5D were approximately 97.4% and 97.9%, respectively. Patients without FN showed longer TtD than patients with FN, in LCSS total score and EQ-5D VAS score. Hazard ratio (HR) (95% CI) for LCSS TtD was 1.71 (1.10-2.65), for EQ-5D VAS score was 3.05 (1.74-5.36), respectively. Patients without FN showed longer TtD than patients with FN in LCSS total score and EQ-5D VAS score. Hazard ratio (HR) (95% CI) for LCSS total score were 0.731 (0.469, 1.147), p=0.0945 (stratified) with censoring rate of 46.0% (with FN) and 54.9% (without FN). For EQ-5D VAS score, HR were 0.82 (0.537, 1.219), p=0.3556 with censoring rate of 32.0% (with FN) and 43.0% (without FN). No significant difference was found. Conclusion: Prevaling clinical opinion suggests that FN negatively impacts QOL. In trial JCWS, a tendency was shown that QOL of patients with FN deteriorates more rapidly than in patients without FN, consistent with current beliefs. Additional investigations is needed but prevention and management of FN may contribute to maintaining QOL.

Keywords: Targeted therapy, antiangiogenesis, advanced NSCLC. Patient reported outcomes (PRO)

P2.03A-024 THE CLINICAL EFFICACY AND SAFETY OF PACLITAXEL LIPOSOEM ON THE PATIENTS WITH NON-SMALL CELL LUNG CANCER: A META-ANALYSIS

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Background: This study was conducted to extract a specific conclusion about the clinical efficacy of paclitaxel liposome in non-small cell lung cancer (NSCLC). Methods: Pubmed, Embase and Chinese National Knowledge Infrastructure (CNKI) databases were searched for potential relevant articles. Relative risks (RRs) with 95% confidence intervals (CIs) represented the influences of paclitaxel liposome on the objective response rate (ORR), disease control rate (DCR) and adverse events. I² and P<0.05 indicate significant heterogeneity. If there existed heterogeneity, then the random-effects model was used. Otherwise, the fixed-effects model was adopted. Sensitivity analysis was performed to test the robustness of overall results. Begg’s funnel plot and Egger’s linear regression test were used to evaluate the potential publication bias. Results: The results indicated that paclitaxel liposome could improve the ORR of NSCLC patients (RR=1.22, 95%CI=1.03-1.43) and enhance DCR as well (RR=1.08, 95%CI=1.01-1.16). The influences of paclitaxel liposome on the incidences of adverse events were analyzed. The outcome suggested that paclitaxel liposome could inhibit the incidences of muscle pain during the therapy (RR=0.34, 95%CI=0.26-0.43). Besides, onset of rash could also be inhibited by paclitaxel liposome (RR=0.17, 95%CI=0.08-0.35). Sensitivity analysis indicated that the overall results were robust. The funnel
Background: The effectiveness and safety of continuation maintenance therapy with pemetrexed versus the watch-and-wait approach was proved by a large randomised phase III trial (Paz-Ares et al., 2013). We focused on continuation maintenance therapy with pemetrexed (Alimta) in routine clinical practice in the Czech Republic. Methods: The primary objective of our analysis was to evaluate the overall survival, defined as the length of time from the start of maintenance therapy to the date of death. Data was summarised using the standard descriptive statistics, absolute and relative frequencies for categorical variables, and the median OS and 95% confidence intervals, as well as median, minimum and maximum values. Kaplan-Meier survival curves were used to display the patient survival. All analyses and graphical outputs were performed in the SAS 9.4 Software. Results: The analysed cohort of NSCLC patients treated with pemetrexed maintenance therapy in the Czech Republic as on March 2016 involved 194 patients. The median age was 64.0 years; stage IV was the predominant clinical stage (84.5%), 52.6% of patients were men, and 47.4% women. Adenocarcinoma was in 190 patients. From a total of 194 patients, treatment response was assessed in 173 patients. Among the assessed patients one showed complete regression (CR), 34 of them (17.9%) showed partial regression (PR), stable disease (SD) was the most frequent response, reported in 95 patients (54.9%); progression occurred in 36 patients (20.8%). Adverse events led to the termination of treatment in only 6 (3.5%) patients. The median number of cycles of maintenance therapy in our study was 5.0 (1.0, 24.0), and the median duration of maintenance therapy was 13.0 weeks. In the registration trial involving 359 patients (Paz-Ares et al., 2013), the continuation maintenance therapy with pemetrexed (Alimta) has been shown to be effective and well tolerated in the Czech population. Treatment had to be terminated only in 6 (3.5%) patients due to adverse events. In the registration trial involving 359 patients (Paz-Ares et al., 2013), the continuation maintenance therapy with pemetrexed led to the median OS of 13.9 months, whereas in the Czech Republic, the median OS has been 15.4 months so far. However, a lower number of patients treated in the Czech Republic must be taken into account, and therefore this result is considered as preliminary.

Keywords: maintenance therapy, NSCLC, advanced diseases, treatment

**P2.03A-025 RANDOMIZED, DOUBLE-BLIND, PHASE 3 STUDY COMPARING BIOSIMILAR CANCER ABP 215 WITH BEVACIZUMAB IN PATIENTS WITH NON-SQUAMOUS NSCLC**

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Background: ABP 215 is a biosimilar candidate that is similar to bevacizumab, a VEGF inhibitor, in analytical and functional comparisons. Pharmacokinetic similarity between ABP 215 and bevacizumab has been demonstrated in a phase I study. Here we present results from a pivotal phase 3 clinical study in non–small-cell lung cancer (NSCLC). Methods: In this double-blind, active-controlled study in adults with non-squamous NSCLC receiving first-line chemotherapy with carboplatin and paclitaxel, subjects were randomized (1:1) to receive investigational product (IP; ABP 215 or bevacizumab 15 mg/kg) Q2W for 6 cycles as an IV infusion. Clinical equivalence was demonstrated by comparing the 2-sided 90% confidence interval (CI) of the ratio of risk (RR) of the objective response rate (ORR; primary endpoint) with pre-specified margin of (0.67, 1.5). Secondary endpoints were risk difference (RD) of the ORR, duration of response (DOR), progression-free survival (PFS), treatment-emergent adverse events (TEAEs), and overall survival (OS). Results: A total of 662 subjects (ABP 215 (Arm 1), n=328; bevacizumab (Arm 2), n=334) were randomized. Demographic and baseline characteristics were balanced between arms. There were 128 (39.0%) responders in Arm 1 and 131 (41.7%) responders in Arm 2. The RR for ORR was 0.93 (90% CI, 0.80–1.09). The RD for ORR was -2.90% (90% CI, -9.26% to 3.45%). Aching the responder rate was 61 (7.5%) in Arm 1 versus 65.5% in Arm 2. The estimated median PFS in Arm 1 was 6.6 months versus 7.9 months in Arm 2; the analysis included all 256 PFS events, 131 (39.9%) in Arm 1 and 125 (38.9%) in Arm 2. The safety population included 324 treated subjects in Arm 1 and 309 in Arm 2; 139 (42.9%) subjects experienced ≥3 TEAEs. TEAEs leading to IP discontinuation affected 61 (18.8%) subjects in Arm 1 and 53 (17.2%) in Arm 2; 25 (26.2%) subjects in Arm 1 and 71 (23.0%) in Arm 2 experienced at least one serious AE; 13 (4.0%) in Arm 1 and 11 (3.6%) in Arm 2 had a fatal TEAE. OS analysis included 79 deaths, 63 (13.3%) in Arm 1 and 36 (11.7%) in Arm 2. Binding antibodies developed during the study in 4 (1.4%) subjects in Arm 1 versus 7 (2.5%) in Arm 2; no subject tested positive for neutralizing antibodies. Conclusion: The study met the primary and secondary objectives demonstrating that ABP 215 and bevacizumab are clinically equivalent.

Keywords: ABP 215, bevacizumab, biosimilar, non-squamous NSCLC

**P2.03A-026 PEMETREXED (ALIMTA) IN MAINTENANCE THERAPY OF 194 PATIENTS WITH ADVANCED NON-SMALL-CELL LUNG CANCER (NSCLC)**

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Background: The effectiveness and safety of continuation maintenance therapy with pemetrexed versus the watch-and-wait approach was proved by a large randomised phase III trial (Paz-Ares et al., 2013). We focused on continuation maintenance therapy with pemetrexed (Alimta) in routine clinical practice in the Czech Republic. Methods: The primary objective of our analysis was to evaluate the overall survival, defined as the length of time from the start of maintenance therapy to the date of death. Data was summarised using the standard descriptive statistics, absolute and relative frequencies for categorical variables, and the median OS and 95% confidence intervals, as well as median, minimum and maximum values. Kaplan-Meier survival curves were used to display the patient survival. All analyses and graphical outputs were performed in the SAS 9.4 Software. Results: The analysed cohort of NSCLC patients treated with pemetrexed maintenance therapy in the Czech Republic as on March 2016 involved 194 patients. The median age was 64.0 years; stage IV was the predominant clinical stage (84.5%), 52.6% of patients were men, and 47.4% women. Adenocarcinoma was in 190 patients. From a total of 194 patients, treatment response was assessed in 173 patients. Among the assessed patients one showed complete regression (CR), 34 of them (17.9%) showed partial regression (PR), stable disease (SD) was the most frequent response, reported in 95 patients (54.9%); progression occurred in 36 patients (20.8%). Adverse events led to the termination of treatment in only 6 (3.5%) patients. The median number of cycles of maintenance therapy in our study was 5.0 (1.0, 24.0), and the median duration of maintenance therapy was 13.0 weeks. In the registration trial involving 359 patients (Paz-Ares et al., 2013), the continuation maintenance therapy with pemetrexed led to the median OS of 13.9 months, whereas in the Czech Republic, the median OS has been 15.4 months so far. However, a lower number of patients treated in the Czech Republic must be taken into account, and therefore this result is considered as preliminary.

Keywords: maintenance therapy, NSCLC, advanced diseases, treatment
**Keywords:** carboplatin, nab-paclitaxel, bevacizumab, Advanced Non-Small Cell and IV Non-Squamous NSCLC

**Background:** The majority of patients (pts) with non-squamous non small cell lung cancer (NSq/NSCLC) present inoperable disease for which no curative treatment exists. The combination of Carboplatin(CBDDCA), Paclitaxel(PTX) and Bevacizumab(BEV) is one of the standards 1st line treatment for this group of pts without EGFR sensitizing mutation or ALK gene rearrangement. The aim of the study was to evaluate the effectiveness and safety of the combination of CBDDCA, PTX and BEV in pts with NSq/NSCLC consecutively admitted and treated in our Dept between 03/2010 and 12/2015. Methods: In a total of 50 pts, 37 men(74%), 13 women(26%), median age 68 (47-82) and ECOG 0-1 pts and 3/10 (30%) for ECOG 2-4, (p = N.S.), 14/34(41%) and 7/16(44%) for pts ≤ 68 vs ≥ 68 years (p = N.S.) respectively. The median PFS was 6+ (1-10+) months for women and 4(2-13) for men. The median OS was 9+ (3-30) months for women and 6(1-24) for men. One out of 50 pts experienced CR for 25 months. The toxicity of the treatment was estimated in a total of 210 cycles of chemotherapy. The most frequent adverse events grade III and IV were neutropenia 2/10 (2.38%), febrile neutropenia 1/10 (0.47%), anemia 5/10 (2.38%) and thrombocytopenia 3/10 (1.43%). Reduction of doses were required only in 6 (12%) pts, in all cases after the 1st or the 2nd cycle of chemotherapy. Hospitalization was required for 4(50%) of the pts., while 1/50 died during a toxic episode. Conclusion: In our selected NSq/NSCLC pts stages IIB or IV the combination of CBDDCA, PTX and BEV with G-CSF prophylaxis was proved effective and very well tolerated independent of EOCG and age. 2. Women seemed to response better than men in this combination.

**Keywords:** NSCLC, chemotherapy, ADVANCED, METASTATIC

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**P2.03A-028 PHASE I/II TRIAL OF CARBOPLATIN, NAB-PACLITAXEL AND BEVACIZUMAB FOR ADVANCED NON-SQUAMOUS NON-SMALL CELL LUNG CANCER: RESULTS OF PHASE I PART**

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**Background:** Nanoparticle albumin-bound paclitaxel (nab-PTX) is a new formulation of paclitaxel and has demonstrated efficacy when combined with carboplatin (Cb), resulting in one of the standard platinum-containing chemotherapy regimens for patients (pts) with chemo-naive advanced non-small cell lung cancer (NSCLC). The addition of anti-vascular endothelial growth factor antibody bevacizumab (BEV) to chemotherapy has been known an effective treatment option for non-squamous NSCLC. The efficacy and safety of the new triplet regimen: Cb + nab-PTX + BEV has not yet been assessed. Methods: We planned multicenter, open-label, phase I/II trial of Cb + nab-PTX + BEV (CARNIVAL study; TORG1426 / LCSG1402). Eligible pts were chemo-naive, aged ≥20 years, ECOG PS 0/1 with advanced non-squamous NSCLC. Pts received 4 to 6 cycles of Cb (AUC = 6, daily) + nab-PTX (dose level 1≤100mg/m2 on days 1, 8 and 15) + BEV (15mg/kg, day1) followed by maintenance nab-PTX + BEV every 3 weeks until disease progression. The phase I part of the study used a 6+6 dose-escalation design to determine the maximum tolerated dose. Major dose-limiting toxicity (DLT) was defined as grade 4 neutropenia for at least 4 consecutive days, febrile neutropenia, grade 4 thrombocytopenia, grade 3-4 non-hematologic toxicity (excluding nausea, vomiting, loss of appetite, fatigue, diarrhea, constipation, disorder of electrolyte, hypertension and hypersensitivity, if they are manageable), and grade 4 hypertension. DLT was assessed during the 1st cycle. This study was registered at UMIN (ID: 000014560). Results: From October 2014 to July 2015, 4 and 12 pts were enrolled at dose level 1 and 2 cohorts respectively. No DLT was observed at either level and recommended phase II dose (RP2D) was determined at dose level 2. Grade ≥3 adverse events (AEs) during the overall treatment period were as follows; neutropenia (32 pts), thrombocytopenia (4 pts), nausea, vomiting, anorexia (3 pts each), anemia, fatigue, hypertension (2 pts each), pneumonia, liver disorder, hypotension, febrile neutropenia, skin ulcer, esophageal perforation (1 pt each). All AEs were manageable. Conclusion: RP2D of Cb + nab-PTX + BEV was determined at dose level 2 (nab-PTX: 100mg/m2 on days 1, 8 and 15 every 3 weeks). We have started phase 2 part of the trial at dose level 2 since November 2015.

**Keywords:** carboplatin, nab-paclitaxel, bevacizumab, Advanced Non-Small Cell Lung Cancer

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**POSTER SESSION 2 — P2.03A: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/IMMUNOTHERAPY CLINICAL TRIALS — TUESDAY, DECEMBER 6, 2016

P2.03A-029 EFFICACY AND SAFETY OF COMBINED CARBOPLATIN,**

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**Background:** Despite a high symptom burden in many patients with advanced NSCLC, limited data exist on QoL with first-line chemotherapy. Here we report results of an interim QoL analysis in patients with SCC NSCLC treated with nab-paclitaxel/carboplatin in the induction part of the ongoing ABOUND. Aim: To evaluate QoL assessments in patients treated with nab-paclitaxel/carboplatin in the induction part of the ongoing ABOUND. Methods: Chemotherapy-naive patients with advanced SCC NSCLC, limited data exist on QoL with first-line chemotherapy. Here we report results of an interim QoL analysis in patients with SCC NSCLC treated with nab-paclitaxel/carboplatin in the induction part of the ongoing ABOUND. ABOUND is a multicenter, open-label, phase IIb study designed to determine the efficacy and safety of nab-paclitaxel/carboplatin as first-line chemotherapy in patients with previously untreated advanced SCC NSCLC. 50 patients were treated for a median of 2 cycles. Patients were assessed using the Lung Cancer Symptom Scale (LCSS) and Euro-QoL-5 Dimensions-5 Levels (EQ-5D-5L). Results: 207 patients were treated on the induction phase. Median age was 68 years; 66% of patients were male, and 99% had an ECOG PS of 0. Out of 200 patients treated for ≥2 cycles, 180 (90%) completed baseline + ≥1 postbaseline QoL assessments. The mean change from baseline in LCSS
CELL LUNG CANCER (NSCLC) PATIENTS UNSUITABLE FOR CHEMOTHERAPY

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Background: Approximately one-third to one-half of all patients with advanced NSCLC presents with a disease that is unsuitable for conventional chemotherapy, both at the first or subsequent lines of treatment. This is mostly due to their very elderly age, poor performance status (PS), to the extent of the disease and/or comorbidities. The prognosis of this patients is extremely poor and no active treatment is often offered. Methods: In a prospective and not randomised study, patients with advanced stage IV histologically confirmed NSCLC who were deemed not eligible to standard chemotherapy because of elderly age (≥ 70 years), and/or poor ECOG PS (≥ 2), and/or extensive brain or bone disease, and/or active comorbidities (≥ 2) requiring pharmacological treatment, were treated with oral metronomic vinorelbine at the fixed dose of 30 mg three times a week until disease progression. Primary endpoint was feasibility, including toxicity and disease control rate (DCR=CR+PR+SD); secondary endpoints included duration of treatment, progression-free survival (PFS) and overall survival (OS) since the start of the treatment. Results: 37 patients, 29 males, 8 females, with a median age of 73 years (range, 50-86), PS=1/2 or 1/3 in 1/28/4/76/22%, stage IVA/IVB in 1/26 (30%), brain/bone disease in 8/13 (22/35%) and a median of 3 (range, 0-5) active comorbidities were treated. Twenty-five patients had an adenocarcinoma (68%), 12 (32%) a squamous cell carcinoma; 2 patients (5%) had an active mutation of the EGFR gene and were previously treated with a TKI. Forty-four patients (38%) received the treatment as first line, 8 (22%) as second line, and 15 (41%) as third or subsequent line. The median cycle of chemotherapy administered was 2 (range, 1-8), G1/G2 toxicities were: anemia in 20 (54%) patients, constipation in 13 (33%), nausea in 9 (26%), anemia in 5 (14%). G3 toxicities were: anemia in 2 (5%) patients, neutropenia and fatigue each in one patient (3%). None patient had G4 toxicity and required dose reduction. Out of the 36 assessable patients, DCR was 25% (in 9 patients). The median duration of treatment was 2.8 months (range, 0-3.8). With a median follow-up of 22.1 months, 3 patients (8%) are still alive; median OS was 5.5 months (range, 5.2-6.1) and median PFS 2.5 months (range, 2.4-2.8). Conclusion: In patients with very poor prognosis advanced NSCLC unsuitable for chemotherapy, oral metronomic vinorelbine may lead to a disease control in a quarter of patients with acceptable toxicities.

Keywords: metronomic, unsuitable, vinorelbine, advanced NSCLC

POSTER SESSION 2 – P2.03A: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/IMMUNOTHERAPY CLINICAL TRIALS – TUESDAY, DECEMBER 6, 2016

P2.03A-033 PREDICTION OF RESPONSE TO FIRST LINE TREATMENT FOR METASTATIC NON-SMALL CELL LUNG CANCER

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Background: Non-small cell lung cancer (NSCLC) is a worldwide problem and usually presents at an advanced stage. Despite widespread availability of multiple chemotherapies for stage IV NSCLC, response rates are generally low. We tried to identify pretreatment factors that may predict response to treatment, particularly relevant in countries with limited laboratory and imaging facilities and drug availability. Methods: We conducted a retrospective analysis of patients with stage IV NSCLC receiving systemic treatment from 2002 to 2012 at the University of Alabama at Birmingham (UAB), which is a NCCN member institute. Pretreatment risk factors including age, race, gender, presenting symptoms, and laboratory values, were evaluated. Patients who originally received adjuvant therapy and no further treatment upon recurrence and those receiving first line treatment on a clinical trial with no further therapy were excluded. Results: 409 patients received more than 10 different regimens as first line treatment in metastatic non-small cell lung cancer. The most commonly used regimens were paclitaxel and carboplatin with or without bevacizumab; Carboplatin and pemetrexed with or without bevacizumab; pemetrexed single agent; Carboplatin and Gemcitabine; and a tyrosine kinase inhibitor. 76.4% of them had a performance status of 0-1 and 21.6% of them has a performance status of 2. More than 50 pretreatment
Background: Despite the success of taxol as an anti-tumor agent, the development of acquired resistance greatly limits its efficacy. A biomarker to predict sensitivity is greatly needed for this agent. The aim of this study was to explore the correlation between the expression of βIII-tubulin/bFGF and taxol chemosensitivity in non–small cell lung carcinoma (NSCLC) A549/Taxol cell lines. Interference effect was detected at mRNA level and protein level respectively by Real Time PCR (RT-PCR) and Western-blot. The cell sensitivity to taxol was examined using MTT assay. Furthermore, apoptosis and cell cycle of A549/Taxol cell lines were tested by flow cytometry. Results: βIII-tubulin and bFGF expression at mRNA level and protein level in NSCLC A549/Taxol cell lines after siRNA transfection were significantly lower than those before transfection. The sensitivity of A549/Taxol cell lines to taxol got a rise by down-regulating βIII-tubulin and bFGF expression. Moreover, it was also found that down-regulation of the two genes significantly increased cell apoptosis and G2/M phase cells percentage.

Conclusion: Down-regulation of either βIII-tubulin or bFGF can sensitize A549/Taxol cells to taxol in vitro. It might be achieved through regulating cell apoptosis and cell cycle. It revealed that the two genes βIII-tubulin and bFGF play critical roles in mediating response to taxol and may serve as novel potential predictive factors for NSCLC therapy.

Keywords: Non-small cell lung carcinoma (NSCLC), Taxol/Paclitaxel, Chemosensitivity
Background: Platinum based chemotherapy is a standard treatment for patients with advanced non-small cell lung cancer (NSCLC) without EGFR mutation or ALK translocation. However, some patients show no response to 1st line treatment. In this study we investigated characteristics and treatment outcome of salvage treatment in this population of advanced NSCLC primary refractory to 1st line chemotherapy including platinum. Methods: We investigated consecutive patients with NSCLC stage IIIIB-IV who received platinum-doublet chemotherapy as a first line treatment between 2014-2015 in a single center. Primary refractory NSCLC was defined as progression free survival (PFS) according to RECIST criteria at the first evaluation. Survival was estimated by Kaplan–meier method. Results: Among 102 patients without known EGFR mutation or ALK translocation who received platinum doublet as 1st line, 13 patients (12.7%) showed PD on the first evaluation of tumor response. Median age was 68 years (range 30-84 years). Five patients had adenocarcinoma, one squamous cell carcinoma, one sarcomatoid carcinoma, and the other five had other histology. First chemotherapy regimen included pemetrexed (n=6), gemcitabine (n=6), and paclitaxel (n=1). Eight of 13 patients received subsequent salvage chemotherapy (gemcitabine based in four, taxane based in three, etoposide+ cisplatin in one) and one patient had no additional response. Three patients had stable disease, one patient showed PD to subsequent chemotherapy, and response could not be evaluated in the other four patients. Median overall survival of the 13 patients was 3.2 months (95% confidence interval 2.3-4.1 months). Conclusion: NSCLC which is primary refractory to 1st line platinum based chemotherapy has a poor survival. The efficacy of other cytotoxic chemotherapy regimens as a salvage treatment was limited. Studies to find an optimal salvage treatment strategy in this population are needed.

Keywords: non-small cell lung cancer, Platinum, refractory, chemotherapy

POSTER SESSION 2 - P.03A: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/IMMUNOTHERAPY CLINICAL TRIALS – TUESDAY, DECEMBER 6, 2016

P.03A-038 PHASE III TRIAL OF Pemetrexed/CARBOPLATIN VS Pemetrexed ONLY IN CHEMO-NAIVE ELDERLY NON-SQCC NSCLC PATIENTS AGED ≥ 70

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Background: We aimed to compare pemetrexed/carboplatin doublet (PC) versus pemetrexed singlet (P) as induction therapy in chemotherapy-naive elderly patients aged 70 or more with advanced non-squamous non–small-cell lung cancer (NSCLC) and an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1. Methods: In this open-label multicenter phase III randomized trial, elderly patients aged 70 or more with advanced non-squamous NSCLC, ECOG PS of 0-1, no prior chemotherapy, adequate organ function and measurable disease were assigned to PC doublet (P, 500 mg/m2; C, area under the curve of 5) or P singlet (500 mg/m2) after stratified randomization according to center, gender and Charson Comorbidity Index (CCI). The treatment was given every 3 weeks till disease progression, unacceptable toxicity or withdrawal of consent. However, carboplatin was included overall survival, response rate, and safety. Results: A total of 267 eligible patients were enrolled from six centers between March 2012 and October 2015; median age was 74 years (70–80); 95% had PS of 0; 68% were men, and 61% had CCI of 1 or more. The median PFS was 5.4 months for PC doublet and 4.2 months for P singlet, respectively (hazard ratio [HR], 0.85; 95% CI, 0.65 to 1.11; P = 0.2353). The median survival time was 12.5 months for PC and 9.0 months for P, respectively (HR, 0.86; 95% CI, 0.62 to 1.21; P =0.4108). The objective response rates for PC doublet and P singlet were 34.7% and 25.9%, respectively (P=0.1387). The most common adverse events in PC doublet arm were anemia (9.2%), fatigue (9.5%) and pneumonia (6.6%) while those in P singlet arm were pneumonia (4.2%), fatigue (3.3%) and anemia (2.5%) in descending of frequency. Conclusion: The addition of carboplatin to pemetrexed during induction therapy period did not show the improvement of survival time in elderly patients aged 70 or more with advanced non–squamous NSCLC and ECOG PS 0-1 even though it increased the response rate numerically. Updated data will be presented.

Keywords: pemetrexed, carboplatin, elderly, chemotherapy-naïve
Background: Retrospective analyses suggest benefit to 2nd line therapy in the fit elderly, but prospective data are lacking. Subgroup analysis of a phase III study of carboplatin and nab-paclitaxel for 1st line treatment of NSCLC showed superior survival in elderly patients. Methods: This is a phase III study for patients ≥70 years of age with progression on a non-taxane 1st line doublet. Nab-paclitaxel 100mg/m² is administered intravenously, 3/4 weeks per cycle until progressive disease or intolerance. The primary endpoint is occurrence of grade 3 treatment-related toxicities after 6 cycles or within 3 weeks if early treatment discontinuation occurred. Null hypothesis is a rate of 60% and alternative hypothesis is ≤ 40%. Results: As of June 2016, 35/42 patients started treatment, and 31 completed. Median age was 75 years (range 70 to 83). 51.4% are female. 8.6% have PS0, 68.6% PS1 and 22.9% PS2. 82.9% have adenocarcinoma, 16.3% squamous, and 2.9% adenosquamous. 5.7% had EGFR, 28.6% kras. 33 patients had one prior treatment and 2 also received nivolumab. Of the 31 patients off treatment, median cycles received was 3 (range 1-22). 11/30 (37%) experienced the primary endpoint. When expanded to >= grade 3 toxicity at any time, this rose to 43% (13/30). The most common toxicities at any time point were fatigue (6/20), peripheral sensory neuropathy (4/30) and neutropenia (3/30). RR was 21% (1CR, 5PR, 16SD and 28.6% RR). RR was 21% (1CR, 5PR, 16SD and 28.6% RR). Conclusion: These results demonstrate efficacy and safety of nab-paclitaxel for the 2nd line treatment of NSCLC in elderly patients and provide prospective data to support the treatment of fit elderly in 2nd line. Updated PFS, OS, geriatric assessment and quality of life data will be presented.

Keywords: elderly, non-small cell lung cancer, nab-paclitaxel
SURVIVAL (OS) AND COSTS IN ELDERLY PATIENTS WITH ADVANCED NSCLC

P2.03A-043 A RETROSPECTIVE ANALYSIS OF THE CHEMOTHERAPY FOR ‘VERY OLD’ PATIENTS AGED 80 YEARS AND ORDER WITH ADVANCED LUNG CANCER

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Background: The number of elderly patients with lung cancer is increasing, and it is becoming a public health problem in Japan. There is little data on the efficacy and safety of chemotherapy for patients aged 80 and older, even though they constitute 30% of all lung cancer incidence (80-84 years, 16%; 85 years and older, 14%) in Japan, and 14.4% in the National Cancer Center, Japan in 2012. Methods: The objective of this study was to evaluate the efficacy and safety of chemotherapy in patients aged 80 and older with advanced lung cancer in our hospital, retrospectively. The medical records were analyzed from January 2010 to July 2016. Results: In total, 27 patients were analyzed. Patient characteristics were as follows: the median ages were 81 years (range, 80-84); female/male: 8/19; PS was 0-1/2; 22/5; adenocarcinoma/squamous/NOS (not otherwise specified)/SCLC: 7/8/1/11, stageIII/IV/0 with: 7/19/5. Platinum-doublets, mono-chemotherapy were used in 15, 12 patients, respectively. In platinum-doublets, the median number of cycle was 3.5 (range 1-13) and dose reduction was conducted in 2 patients (20%). No TRD was observed. The response rate and disease control rate was 8% and 91%, and median PFS was 6.4months (95%CI: 1.8-12.2). Grade 3 or more hematological toxicities tended to be more frequent in platinum-doublets than mono-chemotherapy, but febrile neutropenia was frequent in both groups (neutropenia 93%/75%, thrombocytopenia 33%/0%, febrile neutropenia 20%/33%). After discontinuation of first line therapy, the subsequent chemotherapy was more frequently administered in mono-chemotherapy than platinum-doublets (58% vs 40%). Conclusion: The chemotherapy for patients aged 80 and older could be well tolerated in most cases, but patient selection should be more carefully conducted than in younger patients.

Keywords: chemotherapy, retrospective analysis, advanced lung cancer, patients aged 80 years and older

P2.03A-044 SEVERE ADVERSE EVENTS IMPACT OVERALL SURVIVAL (OS) AND COSTS IN ELDERLY PATIENTS WITH ADVANCED NSCLC

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Background: Among elderly patients with advanced non-small cell lung cancer (NSCLC), treatment beyond first-line therapy may be associated with higher risk of adverse events (AEs) due to patients’ poorer performance status and higher disease burden and comorbidities. This study assessed the impact of severe AEs during second-line (2L) therapy on OS and cost of care in elderly with NSCLC. Methods: Patients aged ≥65 years, diagnosed with advanced NSCLC between 2007-2011 and receiving 2L chemotherapy/targeted therapy, were identified in the SEER-Medicare database (2006-2013). 57 AEs were identified by literature review and consultation with an oncologist. Severe AEs were operationalized as hospitalizations during which a diagnosis for ≥2 AEs was recorded. OS and all-cause healthcare costs post-initiation of 2L chemotherapy/targeted therapy were compared between patients with and without severe AEs. Results: Among 3967 patients initiating 2L, 1624 (44%) had ≥2 severe AEs where hypertension (26%), anemia (24%), and pneumonia (23%) were most commonly reported. Patients with and without severe AEs were similar in demographic and cancer characteristics at diagnosis and 2L treatment regimens; although patients with severe AEs had more comorbidities, notably anemia (69% vs 60%). Median OS for patients with severe AEs was almost half of that for patients without severe AEs (6 vs 11 months). After adjustment for potential confounders, patients with severe AEs had more than double risk of death than patients without severe AEs. Cost of caring for patients with severe AEs was more than twice higher than those patients without severe AEs ($16,135 vs $7,559 per-patient-per-month).

Conclusion: Occurrence of severe AEs among elderly non-SCLC patients who are receiving 2L chemotherapy/targeted therapy is associated with worse clinical outcomes and a higher economic burden. Results of this analysis suggest that better tolerated therapies may improve outcomes for patients and reduce cost to the healthcare system.

Keywords: second-line chemotherapy, overall survival and healthcare costs, adverse events, advanced NSCLC

P2.03A-045 SAFETY OF BEVACIZUMAB (B) IN ELDERLY STAGE IV NON-SQUAMOUS NSCLC PATIENTS SELECTED BY GERIATRIC ASSESSMENT: A PHASE II STUDY

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Background: The number of elderly patients treated with Platinum-doublet chemotherapy in first-line treatment for non-squamous NSCLC showed improvement of progression free survival (PFS) and overall survival (OS) (ECOG 4539). However, in a subset analysis of this trial, grade 3 to 5 toxicities occurred more frequently in elderly patients treated with CPB compared with patients treated with

Keywords: elderly, lung cancer, comorbidity
CP and in elderly patients compared with younger patients. Grade 3/4 neutropenia was 34% in elderly patients. GIDO2101 was the first trial addressed specifically to assess the safety of B in chemotherapy patients. We hypothesized that an adjusted dose-regimen administered to elderly patients selected by an adapted geriatric assessment could reduce the rate of neutropenia to 20%. Methods: Elderly (≥70 years old) chemotherapy-naive stage IIIb/IV or recurrent non-squamous NSCLC patients, ECOG-PS 0-1, measurable target lesion, and adequate organ functions were eligible for this study. After an Adapted Geriatric Assessment, elderly patients with NSCLC received a modified regimen consisting on triweekly CAUC + P 175 mg/m² + B 7.5 mg/kg. Results: Twenty-six eligible patients (20 male, 6 female, median age, 76 years) were enrolled between August 2013 and June 2015. Six and 20 patients had ECOG-PS of 0 and 1, respectively. The median number of CPB treatment cycles received was ≥2. 70% patients (66%) received B maintenance (median number of cycles 7). At the time of analysis, 3 patients are still on treatment. Grade 3/4 neutropenia was observed only in one patient (3.8%).

Grade 3/4 non-haematological and haematological toxicities were observed in 10 (38.5%) and 4 (15.4%), pts, respectively. The most common grade 3/4 AEs included anaemia (11.5%) and hypertension (15.4%). One fatal AE was observed. At the time of this preliminary analysis, median PFS was 8.22 months (6.0-10.3) and median OS was 11.6 (8.0-15.1). Conclusion: CPB triweekly followed by BEV showed an acceptable toxicity profile with a favourable grade 3-4 neutropenia of 3.8% compared with previously reported. Efficacy of this first-line regimen for selected elderly non-squamous NSCLC patients was similar to younger patients. However, this study has the limitation of the small number of patients, although a simple size of 51 patients was needed to test this hypothesis, the study was halted after the inclusion of 26 patients due to the slow recruitment.

Keywords: elderly, bevacizumab, NSCLC, Geriatric assessment

QoL measured by LCSS and EQ-5D-SL remained stable or improved through 4 cycles. Conclusion: This interim analysis from ABOUND.70+ demonstrated promising activity and tolerability of nab-paclitaxel/carboplatin regimens in elderly patients with advanced NSCLC similar to prior phase III data. NCT02151169

Keywords: Safety, efficacy, elderly, nab-paclitaxel
Abstracts

TUESDAY, DECEMBER 6, 2016
CLINICAL TRIALS – POSTER SESSION 2 – P2.034: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/ IMMUNOTHERAPY
CLINICAL TRIALS - TUESDAY, DECEMBER 6, 2016

P2.034-049 RESPONSE TO SALVAGE CHEMOTHERAPY FOLLOWING EXPOSURE TO PD-1 INHIBITORS IN PATIENTS WITH NON-SMALL CELL LUNG CANCER
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Background: Programmed death-1 (PD-1) inhibitors are effective second line treatment in non-small cell lung cancer (NSCLC), however objective responses are seen in only 20-30% of patients. While a minority of patients achieve durable response to PD-1 inhibitors, those who progress or are refractory receive salvage chemotherapy. We evaluate response to salvage chemotherapy following exposure to PD-1 inhibitors. Methods: Eligible patients were adults with NSCLC followed at the Vanderbilt Cancer Center or the academic Winship Cancer Center undergoing salvage chemotherapy following PD-1 inhibitors (cases) versus no PD-1 inhibitors (controls). CT-imaging of the chest/abdomen/pelvis was done within 4 weeks of initiation of salvage chemotherapy and every 6 weeks thereafter. Revised RECIST guidelines were used to define response to treatment. Clinical and imaging data were abstracted from electronic medical records. Multivariate logistic regression analysis was used to calculate probability of response. Results: Three hundred patients’ charts were reviewed and 56 patients met eligibility criteria. Among evaluable patients, 28 were males versus 28 females. Median age was 61.64 years (interquartile ranges (IQR): 55.33–69.36) in cases versus 67.82 (IQR: 54.08–72.24) in controls. Forty-one patients were classified as cases versus 15 controls. Thirty-six patients received nivolumab and 5 pembrolizumab. Forty-five (80%) patients had adenocarcinoma, 10 (18%) squamous cell carcinoma and 1 (2%) large cell carcinoma. The median number of chemotherapy regimens prior to salvage chemotherapy was 3 (IQR: 2-3) in cases versus 2 (IQR: 1-2) in controls. The drugs most commonly used in salvage regimens included docetaxel, pemetrexed, paclitaxel, gemcitabine. Seven (17%) cases had partial response to chemotherapy versus 16.6% (5/30) in controls. Eleven (27%) cases had progressive disease versus 6 (40%) controls. Twenty-three (56%) cases had stable disease versus 8 (53%) controls. The odds ratio for achieving a partial response was 0.16 (95% CI: 0.08 to 0.35, P=0.001). In multiple logistic regression model, age, gender, number of prior chemotherapy regimens, tumor histology, smoking status, different salvage chemotherapy regimens were not associated with the likelihood of achieving a partial response. Conclusion: The odds of achieving a partial response to salvage chemotherapy were 6 times higher in patients with prior exposure to PD-1 inhibitors. This observed difference however warrants confirmation in larger cohorts. If confirmed, this difference may represent an argument to promote immune PD-1 inhibitors as first line regimen for the treatment of NSCLC not amenable to targeted therapy.

Keywords: PD-1, non-small cell lung cancer, salvage chemotherapy

POSTER SESSION 2 – P2.035: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/ IMMUNOTHERAPY
CLINICAL TRIALS - TUESDAY, DECEMBER 6, 2016

P2.035-050 ELEVATED EXPRESSION OF CCP GENES IS ASSOCIATED WITH ABSOLUTE CHEMOTHERAPY BENEFIT IN EARLY STAGE LUNG ADENOCARCINOMA PATIENTS
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Background: A validated RNA molecular expression signature based on cell cycle progression (CCP) genes (CCP score) and a molecular Prognostic Score (mPS) combination of CCP score and pathological stage are significant prognostic markers of cancer-specific mortality in patients with early stage lung adenocarcinoma. Additionally, preliminary data suggest a significant association between CCP score and absolute benefit with platinum-based adjuvant chemotherapy in early stage lung adenocarcinoma patients. The aim of this study is to further demonstrate the effectiveness of CCP score and mPS in predicting platinum-based chemotherapy benefit in a large, multi-institutional cohort of stage IB and IIA lung adenocarcinoma patients who underwent definitive surgical resection with and without adjuvant chemotherapy. Methods: Formalin-fixed paraffin-embedded surgical tumor samples have been accrued from 388 patients treated with a platinum-based chemotherapy (n = 400) and without (n = 600) will be analyzed samples from approximately 1000 patients diagnosed with stage IB and IIA lung adenocarcinoma who underwent definitive surgical treatment with adjuvant platinum-based chemotherapy (n = 400) and without (n = 600) will be analyzed for 31 proliferation genes by quantitative RT-PCR. The associations of CCP score and mPS with absolute benefit from platinum-based chemotherapy will be separately examined using Cox proportional hazards regression with an outcome of 5-year lung cancer survival. Results: To date, lung tumor samples have been accrued from 388 patients treated with a platinum-based chemotherapy and 590 untreated patients. We hypothesized that the absolute treatment benefit will increase as CCP score or mPS increases. Results will be shown for continuous CCP score and mPS as well as pre-defined binary CCP score and binary mPS. Conclusion: This study will determine the abilities of CCP score and mPS as predictive tools for absolute chemotherapy benefit and 5-year lung cancer survival in patients with early stage lung adenocarcinoma thereby furthering the clinical utility for these signatures to identify patients with high risk disease who should receive adjuvant chemotherapy.

Keywords: CCP, mPS, lung cancer, early stage, adjuvant chemotherapy

POSTER SESSION 2 – P2.038: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/ IMMUNOTHERAPY
CLINICAL TRIALS - TUESDAY, DECEMBER 6, 2016

P2.038-051 CMTM1, V17 PROMOTES CHEMOTHERAPY RESISTANCE AND IS ASSOCIATED WITH POOR PROGNOSIS IN NON-SMALL CELL LUNG CANCER
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Background: Small cell lung cancer (SCLC) is an aggressive form of lung cancer characterized by loss of the tumor suppressor Rb. Chemotherapy remains the standard of care for SCLC patients but produces severe myelosuppression that compromises patient outcomes. G1T28 is a potent and selective CDK4/6 inhibitor in development to reduce chemotherapy-induced myelosuppression and preserve immune system function in SCLC patients. Cyclin dependent kinases 4 and 6 (CDK4/6) phosphorylate Rb protein promoting proliferation of specific cell types such as hematopoietic stem progenitor cells (HSPCs) by allowing cells to progress through G1 to S phase. HSPCs are exquisitely dependent upon CDK4/6 for proliferation and become arrested in the G1 phase of the cell cycle upon exposure to G1T28. We hypothesize that G1T28-mediated CDK4/6 inhibition may selectively protect immune cells (Rb intact) from chemotherapy without antagonizing the antitumor efficacy in Rb deficient tumors, such as SCLC. G1T28 preservation of adaptive immunity from cisplatin-induced cytotoxicity may enhance the efficiency of chemotherapy in SCLC tumors by allowing a more robust host immune response. Methods: Syngeneic mouse models were established by flank injection of KPI and TKO/Gm murine cells derived from TP53 and RB1 or TP53, RB1 and P130 mutant mice respectively. When tumors reached 150mm3, mice were randomized and treated with G1T28, cisplatin and combination of both. Tumor volumes were measured and immune populations from tumor, spleen, and peripheral blood were analyzed by flow cytometry. Results: CDK4/6 inhibition by G1T28 protects peripheral white blood cells (lymphocytes, monocytes and eosinophils) from cisplatin-induced cytotoxicity in the syngeneic SCLC KPI mouse model. Additionally, treatment with G1T28 prior to cisplatin results in tumor shrinkage in syngeneic Rb deficient mice (66% versus 12%, respectively) in the syngeneic SCLC TKO/Gm mouse model. Conclusion: G1T28-mediated CDK4/6 inhibition protects immune cells from chemotherapy and potentiates the reduction of tumor volume when combined with cisplatin in a syngeneic Rb deficient SCLC mouse model. Studies are ongoing to determine if the immune protection by G1T28 is enhancing the anti-tumor activity of cisplatin in this model, as well as to evaluate other potential mechanisms. Additionally, clinical trials testing the combination of G1T28 with chemotherapy in patients with extensive stage SCLC are currently in progress (1st line, carboplatin-etoposide, NCT02497770; 2nd line, topotecan, NCT02514447).

Keywords: CDK4/6-mediated inhibition, immune protection, small cell lung cancer, chemotherapy

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Background: Despite a consistent rate of initial responses, chemotherapy treatment often results in the development of chemoresistance, leading to therapeutic failure in non-small cell lung cancer (NSCLC). CMTM1_v17 is highly expressed in human testis tissues and solid tumor tissues but relatively low expression was observed in the corresponding normal tissues. This study aims to investigate the significance of CMTM1_v17 in NSCLC and its association with cisplatin-based neo-adjuvant chemotherapy (NAC) response.

Methods: 31 pairs of tumor tissues before and after NAC and 78 resected tumor tissues after NAC were utilized for immunohistochemistry (IHC) staining of CMTM1_v17 protein. Flow cytometry was used to detect the change of CMTM1_v17 expression in NSCLC patient-derived xenografts (PDX) models with cisplatin treatment. Results: CMTM1_v17 expression was found to be significantly related to treatment effect and outcome in the tumor tissues after NAC but not in the tissues before NAC from the 31 cases of NSCLC. We identified that high CMTM1_v17 expression was associated with low objective remission rate (ORR) (p<0.008) and poor prognosis (the median OS: 35.1 months vs 65.6 months p=0.0045, the median DFS: 17.27 months vs 35.54 months p=0.0207) in the 31 patients. Next, we detected CMTM1_v17 expression to confirm correlation between this protein status and clinical characteristics in 78 NSCLC patients with NAC. The up-regulation of CMTM1_v17 had a higher SD rate (p=0.007) and worse outcome (the median OS: 41.0 months vs 80.6 months, p=0.0028, the median DFS: 33.4 months vs 64.8 months p=0.0032). Cox multivariate analysis indicated that CMTM1_v17 is an independent prognostic risk factor on patients who received NAC (HR=3.642, p=0.002). DFS HR=2.867 p=0.003). Then, we tested CMTM1_v17 expression in the lung cancer PDX mice with different treatment, showing that this protein was up-regulated in the tumor tissues received cisplatin treatment, compared to the tumor tissues without cisplatin treatment of control group. Conclusion: CMTM1_v17 expression was significantly associated with chemoresistance and poor prognosis of the early stage NSCLC patients who received NAC. Cisplatin could induce the expression of CMTM1_v17 in lung cancer cells from PDX model.

Keywords: non-small cell lung cancer, CMTM1_v17, Cisplatin, neo-adjuvant chemotherapy.
U.S. COOPERATIVE GROUP TRIALS

Background: Neutropenia is the most serious hematologic toxicity associated with the use of chemotherapy. Severe neutropenia (SN) may result in dose delays and/or reductions, and the use of growth colony stimulating factors (CSF) or dose increases may be needed only in patients in whom SN was identified as a frequent problem. The lymphoma model (LM) was published in 2013 to predict individual risk of neutropenia in patients receiving chemotherapy for multiple types of cancer. The LM model has not been validated by external datasets. We investigated the LM with a large external lung cancer dataset based on clinical criteria of SN and investigated new risk prediction models for SN. Methods: Stata/IC version 14 was used for small cell lung cancer (NSCLC) and extensive small cell lung cancer (SCLC). Chemotherapy phase II/III trials completed in 1990-2012 were assembled from U.S. cancer cooperative groups. SN was defined as any neutropenic complications (grade 3 or 4) according to CTCAE. A risk score was calculated as a weighted sum of regression coefficients of the LM for all patients in the database. The performance of risk models was evaluated by the area under the ROC curve (AUC) with a good model defined as AUC ≥ 0.7. To develop new risk models, a random split was used to divide the database into training cohort (2/3) and testing cohort (1/3). Multivariable logistic regression models with stepwise selection and lasso selection (Tibshirani, 1996) were built in training cohort and validated in testing cohort. Candidate predictors included patient-level and treatment-level variables. The patients with complete data were used for validation and all patients, including those with imputed predictors, were used to develop new risk models. Results: Eighty seven trials with 14,829 patients were included. The LM had a good performance in SCLC patients (AUC = 0.86, 95% confidence interval, 0.80 to 0.91) with the median dose intensity was 89.1 mg/m2 per week. Hematologic toxicities of grade 3 or 4 included neutropenia (19.5%) and leucopenia (17.1%), with no cases of febrile neutropenia being observed. Individual nonhematologic toxicities of grade 3 or 4 included mucositis (3.2%), peripheral neuropathy (2.8%) and asymptomatic elevation in AST (3.2%). Weekly nab-paclitaxel was associated with acceptable toxicity and a favorable overall response rate (ORR) of 19.3% (95% confidence interval, 9.1%-36.2%). Conclusion: The LM model had good performance in SCLC patients and could be useful for risk assessment. Keywords: severe neutropenia, risk prediction models, validation, chemotherapy

Poster Session 2 – P.02.03A Advanced NSCLC & Chemotherapy/Targeted Therapy/Immunotherapy Clinical Trials – Tuesday, December 6, 2016

P.02.03A-055 PREDICTING RISK OF CHEMOTHERAPY-INDUCED SEVERE NEUTROPENIA IN LUNG PATIENTS: A POOLED ANALYSIS OF US COOPERATIVE GROUP TRIALS

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Background: Neutropenia is the most serious hematologic toxicity associated with the use of chemotherapy. Severe neutropenia (SN) may result in dose delays and/or reductions, and the use of growth colony stimulating factors (CSF) or dose increases may be needed only in patients in whom SN was identified as a frequent problem. The lymphoma model (LM) was published in 2013 to predict individual risk of neutropenia in patients receiving chemotherapy for multiple types of cancer. The LM model has not been validated by external datasets. We investigated the LM with a large external lung cancer dataset based on clinical criteria of SN and investigated new risk prediction models for SN. Methods: Stata/IC version 14 was used for small cell lung cancer (NSCLC) and extensive small cell lung cancer (SCLC). Chemotherapy phase II/III trials completed in 1990-2012 were assembled from U.S. cancer cooperative groups. SN was defined as any neutropenic complications (grade 3 or 4) according to CTCAE. A risk score was calculated as a weighted sum of regression coefficients of the LM for all patients in the database. The performance of risk models was evaluated by the area under the ROC curve (AUC) with a good model defined as AUC ≥ 0.7. To develop new risk models, a random split was used to divide the database into training cohort (2/3) and testing cohort (1/3). Multivariable logistic regression models with stepwise selection and lasso selection (Tibshirani, 1996) were built in training cohort and validated in testing cohort. Candidate predictors included patient-level and treatment-level variables. The patients with complete data were used for validation and all patients, including those with imputed predictors, were used to develop new risk models. Results: Eighty seven trials with 14,829 patients were included. The LM had a good performance in SCLC patients (AUC = 0.86, 95% confidence interval, 0.80 to 0.91) with the median dose intensity was 89.1 mg/m2 per week. Hematologic toxicities of grade 3 or 4 included neutropenia (19.5%) and leucopenia (17.1%), with no cases of febrile neutropenia being observed. Individual nonhematologic toxicities of grade 3 or 4 included mucositis (3.2%), peripheral neuropathy (2.8%) and asymptomatic elevation in AST (3.2%). Weekly nab-paclitaxel was associated with acceptable toxicity and a favorable overall response rate (ORR) of 19.3% (95% confidence interval, 9.1%-36.2%). Conclusion: The LM model had good performance in SCLC patients and could be useful for risk assessment. Keywords: severe neutropenia, risk prediction models, validation, chemotherapy

Poster Session 2 – P.02.03A Advanced NSCLC & Chemotherapy/Targeted Therapy/Immunotherapy Clinical Trials – Tuesday, December 6, 2016

P.02.03A-057 LIGAND MEDIATED SOLID LIPID NANOPARTICLE OF PACLITAXEL FOR EFFECTIVE MANAGEMENT OF BRONCHOGENIC CARCINOMA

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Background: Lung cancer is a disease of uncontrolled cell growth in tissues of lung. It is most common cause of cancer-related deaths in men and second most common in women. It is responsible for 1.3 million deaths worldwide annually. Most common cause is long term exposure to tobacco smoke. The occurrence of lung cancer in nonsmokers, who accounts 15% cases, attributed to combination of genetic factors, radon gases, and asbestos and air pollution including second hand smoke. Methods: The treatment and management of diseases associated with lung is difficult with presently available therapeutic systems, as insufficient drug reaches to lung due to mucocilliary clearance of the medication. The proposed drug delivery system was used to determine targeting efficacy of optimized formulation via conjugation of ligand to Solid Lipid Nanoparticles (SLNs) bearing paclitaxel anchored with lactoferrin molecules. These systems may enhance the drug delivery to lung via receptor mediated endocytosis mechanism Results: The SLNs were prepared by modified Solvent Injection Method, and then sonicated and finally ligand anchored. The nanoparticles were characterized in-vitro for their shape and size by Scanning (SEM) & Transmission Electron Microscopic (TEM), Drug entrapment, in-vitro drug release and stability. The in-vivo study
Background: LCL161, a novel Smac mimetic, is known to have anti-tumor activity and improve chemosensitivity in various cancers. However, the function and mechanisms of the combination of LCL161 and paclitaxel in non-small cell lung cancer (NSCLC) remain unknown. Methods: Cellular inhibitor of apoptotic protein 1 and 2 (cIAP1 and cIAP2) expression in NSCLC tissues and adjacent non-tumor tissues were assessed by immunohistochemistry. The correlations between cIAP1, 2 expression and clinicopathological characteristics, prognosis were analyzed. Cell viability and apoptosis were measured by MTT assays and Annexin V-FITC assay. Western blot and co-immunoprecipitation assay were performed to measure the protein expression and interaction in NF-κB pathway. siRNA mediated gene silencing and caspases activity assays were applied to demonstrate the role and mechanisms of cIAP1,2 and RIP1 in lung cancer cell apoptosis. Mouse xenograft NSCLC models were used in vivo to determine the therapeutic efficacy of LCL161 alone or in combination with paclitaxel. Results: The expression of cIAP1 and cIAP2 in Non-small cell lung cancer (NSCLC) tumors was significantly higher than that in adjacent normal tissues. cIAP1 was highly expressed in patients with late TNM stage NSCLC and a poor prognosis. Positive for cIAP1 and cIAP2 was an independent prognostic factor that indicated a poorer prognosis in NSCLC patients. LCL161, an IAP inhibitor, cooperated with paclitaxel to reduce cell viability and induce apoptosis in NSCLC cells. Molecular studies revealed that paclitaxel increased TNFα expression, thereby leading to the recruitment of various factors and the formation of the TRADD-TRA2-RIP1-cIAP complex. LCL161 degraded cIAP1 and cIAP2, releasing RIP1 from the complex. Subsequently, RIP1 was stabilized and bound to caspase-8 and FADD, thereby forming the caspase-8/RIP1/FADD complex, which activated caspase-8, caspase-3 and ultimately lead to apoptosis. In nude mouse xenograft experiments, the combination of LCL161 and paclitaxel degraded cIAP1,2, activated caspase-3 and inhibited tumor growth with few toxic effects. Conclusion: Thus, LCL161 could be a useful agent for the treatment of NSCLC in combination with paclitaxel.

Keywords: NSCLC, paclitaxel, apoptosis, LCL161
**P2.03A-061 RANDOMIZED PHASE II TRIAL COMPARING INTERCALATION OF AFATINIB TO PEMETREXED WITH PEMETREXED ALONE AFTER FAILURE OF PLATINUM DOUBLET THERAPY**

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Background: The combination of pemetrexed and erlotinib was synergistic in non-small cell lung cancer in vitro, if erlotinib exposure was avoided before pemetrexed. To enhance the efficacy of 1st-line pemetrexed, we designed to test the sequential administration of afatinib followed by pemetrexed (pem+afa) compared with pemetrexed (pem) monotherapy. Methods: We performed randomized phase II trial in Asian Medical Center, Seoul, Korea. Patients with histologically or cytologically confirmed as non-squamous lung cancer were enrolled. Patients were stratified by response to 1st-line treatment and smoking history, and randomly assigned in a 2:1 ratio to receive intravenous pemetrexed (500 mg/m2) on D1 followed by afatinib 40 mg/day on D2-15 or pemetrexed (500 mg/m2) on D1 every 3 weeks. The treatment was continued until disease progression. Primary end point was objective response rate (ORR), and secondary end points were progression-free survival (PFS) and overall survival (OS). Results: From August 2012 to July 2016, a total 87 patients (male, 71.3%; never smoker 31.0%; sensitive to 1st-line therapy (PR+S0) 65.5%; median age 59 years) were randomized to pem (n=30) or pem+afa (n=57). Median follow-up duration was 12.4 months (range, 0.4-46.6 months). Median cycles administered were both 4 cycles in each group (range, 2-8 in pem group; 1-62 in pem+afa group). Among 57 patients in pem+afa group, 26 patients (45.6%) underwent dose reduction (30 mg/ day in 18 patients, 20 mg/day in 8 patients). By July, 2016, among 81 evaluable patients, 22 responses were noticed (4 in pem group; 18 in pem+afa group). ORR were 13.3% (6/30) and 31.6% (18/57) in pem and pem+afa, respectively (2-sided p-value<0.07). Median PFS were 2.9 months and 5.7 months in pem and pem+afa, respectively (HR:0.718; 95% CI, 0.427-1.148; p=0.163). Median OS were 15.6 months and 12.1 months in pem and pem+afa, respectively (HR:1.393; 95% CI, 0.794-2.445; p=0.245). Conclusion: Intercalation of afatinib to pemetrexed looks better in numerically but statistically insignificant compared with pemetrexed monotherapy in 2nd-line treatment in EGFR unselected population with non-squamous lung cancer.

Keywords: pemetrexed, afatinib, non-squamous lung cancer, intercalation

**P2.03A-062 CHARACTERISATION AND TARGETING OF THE DNA REPAIR GENE, XRC6BP1, IN CISPLATIN RESISTANT NSCLC**

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Background: In the presence and absence of 1μM BBI608, DNA repair capacity was assessed using enhanced α-H2AX foci in response to cisplatin. Before and after treatment with BBI608, CisR subpopulations were selected using Aldefluor and flow cytometry analysis of an isogenic panel of matched parent (PT) and cisplatin resistant (CisR) NSCLC cell lines. CisR cells were isolated using a combination of Aldefluor, stem cell markers and 1μM BBI608. The ability of BBI608 to induce apoptosis was assessed using flow cytometry and Annexin V-PI staining.

Methods: BBI608 in vitro and in vivo models of pancreatic and prostate cancer have shown promise. Methods: Aldefluor (Stemcell Technologies) staining and flow cytometry analysis of an isogenic panel of matched parent (PT) and cisplatin resistant (CisR) NSCLC cell lines identified the ALDH1-positive (ALDH1+ve) CSC subpopulation of cells as a key CSC subset across cisplatin resistant NSCLC cell lines. PT and CisR cell lines were treated with BBI608 (1μM) and stemness factors investigated, the presence of the ALDH1+ve CSC population was reassessed by flow cytometry and expression of stemness factors (Nanog, OCT3/4, Sox2, Klf4 and cMyc) were examined by reverse transcriptase PCR. The functional parameters of proliferation, clonogenic survival and apoptosis were investigated by increasing concentrations of cisplatin (0-100μM) in the presence and absence of 1μM BBI608. Results: The NSCLC CisR sublines showed a significantly greater ALDH1+ve CSC population relative to their PT counterparts. Treatment of the CisR sublines with 1μM BBI608 significantly depleted the ALDH1+ve CSC population and decreased gene expression of stemness markers. BBI608 significantly decreased the proliferative capacity and clonogenic survival of the CisR sublines when in combination with cisplatin relative to cisplatin alone. Cisplatin in combination with BBI608 significantly increased cisplatin-induced apoptosis in the CisR sublines indicating restoration of cisplatin sensitivity. Conclusion: To date, BBI608 has not been investigated in terms of a cisplatin resistant CSC population in lung cancer. BBI608, via the inhibition of STAT3, pharmacologically depleted the CSC subpopulation of cells as a key CSC subset across cisplatin resistant NSCLC cell lines. PT and CisR cell lines were treated with BBI608 (1μM) and stemness factors investigated, the presence of the ALDH1+ve CSC population was reassessed by flow cytometry and expression of stemness factors (Nanog, OCT3/4, Sox2, Klf4 and cMyc) were examined by reverse transcriptase PCR. The functional parameters of proliferation, clonogenic survival and apoptosis were investigated by increasing concentrations of cisplatin (0-100μM) in the presence and absence of 1μM BBI608. Results: The NSCLC CisR sublines showed a significantly greater ALDH1+ve CSC population relative to their PT counterparts. Treatment of the CisR sublines with 1μM BBI608 significantly depleted the ALDH1+ve CSC population and decreased gene expression of stemness markers. BBI608 significantly decreased the proliferative capacity and clonogenic survival of the CisR sublines when in combination with cisplatin relative to cisplatin alone. Cisplatin in combination with BBI608 significantly increased cisplatin-induced apoptosis in the CisR sublines indicating restoration of cisplatin sensitivity. Conclusion: To date, BBI608 has not been investigated in terms of a cisplatin resistant CSC population in lung cancer. BBI608, via the inhibition of STAT3, pharmacologically depleted the CSC subpopulation and stemness expression while simultaneously restoring cisplatin sensitivity. There are currently a number of clinical trials recruiting patients to further investigate BBI608. These data suggest a promising role for BBI608 in the treatment of non-responsive or recurrent NSCLC.

Keywords: Cancer Stem Cells, BBI608, Cisplatin resistance, aldehyde dehydrogenase 1
OPEN-LABEL, NONRANDOMIZED STUDY
P2.03A-065 INHIBITION AND EXPLOITATION OF ALDEHYDE DEHYDROGENASE 1 AS A CANCER STEM CELL MARKER TO OVERCOME CISPLATIN RESISTANT NSCLC
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Background: The root of therapeutically resistant hypothesized to be the presence a rare CSC population within the tumour population which survives chemotherapeutic treatment and has the potential to recapitulate a heterogeneous tumour. Aldehyde dehydrogenase 1 (ALDH1) is involved the catalytic conversion of vitamin A (retinoic acid) and has been identified as a CSC marker in a number of solid malignancies. Methods: FACS analysis of an isogenic panel of matched parent (PT) and cisplatin resistant (CisR) NSCLC cell lines identified ALDH1 as a promising CSC marker associated with cisplatin resistance across NSCLC histologies. The C61780 CisR subline was separated by FACS into ALDH1-positive and negative subpopulations and subcutaneously injected into NOD/SCID mice to assess tumour initiation and growth. ALDH1 was inhibited in vitro within the cell lines using two pharmacological ALDH1 inhibitors, DEAB and disulfiram, alone and in combination with cisplatin. Cell lines were treated with cisplatin and retinol and all-trans retinoic acid (ATRA) to exploit the vitamin A/retinoic acid axis in which ALDH1 is involved. Results: The CisR sublines showed significantly greater ALDH1 activity relative to their PT counterparts. In vivo subcutaneous injection of ALDH1-positive and negative subpopulations revealed no significant difference in tumour initiation or growth rate. ALDH1 inhibition in combination with cisplatin significantly decreased clonogenic cellular growth and proliferative competencies and increased apoptosis cell death compared to cisplatin alone. Vitamin A supplementation and ATRA treatment in combination with cisplatin showed similar re-sensitising effects. Conclusion: This pharmacological CSC depletion in conjunction with cisplatin treatment resulted in re-sensitisation of cisplatin resistant cells to the cytotoxic effects of cisplatin. These data suggest vitamin A supplementation or the addition of ATRA or an ALDH1 inhibitor to the cisplatin-based chemotherapeutic regimen may be of clinical benefit in overcoming tumour recurrence and cisplatin resistance.

Keywords: Vitamin A, ATRA, Ciplatin resistance, Cancer Stem Cells

POSTER SESSION 2 – P2.03A: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/IMMUNOTHERAPY
CLINICAL TRIALS – TUESDAY, DECEMBER 6, 2016
P2.03A-064 INHIBITION AND EXPLOITATION OF ALDEHYDE DEHYDROGENASE 1 AS A CANCER STEM CELL MARKER TO OVERCOME CISPLATIN RESISTANT NSCLC
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Background: The root of therapeutically resistant hypothesized to be the presence a rare CSC population within the tumour population which survives chemotherapeutic treatment and has the potential to recapitulate a heterogeneous tumour. Aldehyde dehydrogenase 1 (ALDH1) is involved the catalytic conversion of vitamin A (retinoic acid) and has been identified as a CSC marker in a number of solid malignancies. Methods: FACS analysis of an isogenic panel of matched parent (PT) and cisplatin resistant (CisR) NSCLC cell lines identified ALDH1 as a promising CSC marker associated with cisplatin resistance across NSCLC histologies. The C61780 CisR subline was separated by FACS into ALDH1-positive and negative subpopulations and subcutaneously injected into NOD/SCID mice to assess tumour initiation and growth. ALDH1 was inhibited in vitro within the cell lines using two pharmacological ALDH1 inhibitors, DEAB and disulfiram, alone and in combination with cisplatin. Cell lines were treated with cisplatin and retinol and all-trans retinoic acid (ATRA) to exploit the vitamin A/retinoic acid axis in which ALDH1 is involved. Results: The CisR sublines showed significantly greater ALDH1 activity relative to their PT counterparts. In vivo subcutaneous injection of ALDH1-positive and negative subpopulations revealed no significant difference in tumour initiation or growth rate. ALDH1 inhibition in combination with cisplatin significantly decreased clonogenic cellular growth and proliferative competencies and increased apoptosis cell death compared to cisplatin alone. Vitamin A supplementation and ATRA treatment in combination with cisplatin showed similar re-sensitising effects. Conclusion: This pharmacological CSC depletion in conjunction with cisplatin treatment resulted in re-sensitisation of cisplatin resistant cells to the cytotoxic effects of cisplatin. These data suggest vitamin A supplementation or the addition of ATRA or an ALDH1 inhibitor to the cisplatin-based chemotherapeutic regimen may be of clinical benefit in overcoming tumour recurrence and cisplatin resistance.

Keywords: Vitamin A, ATRA, Ciplatin resistance, Cancer Stem Cells

POSTER SESSION 2 – P2.03A: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/IMMUNOTHERAPY
CLINICAL TRIALS – TUESDAY, DECEMBER 6, 2016
P2.03A-066 PEMETREXED(P) IN THIRD AND FOURTH LINE CHEMOTHERAPY FOR ADVANCED NON-SMALL CELL LUNG CANCER (NON-SQUAMOUS)-ANSCLCNS
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Background: Platinum-based chemotherapy remains the standard first-line treatment for a NSCLC. A standard for second-line chemotherapy could be docetaxel or pemetrexed. Third and fourth line of chemotherapy is not defined. Methods: Patients (Pt.) were included in the study. Pt. were enrolled successively by the date of coming into the clinic All Pt had assessment of response after 2-3 cycles of chemotherapy. First line consisted of: P plus carboplatin. P in mono-therapy was used in second, third and fourth line. 26 Pt. (Group A) were evaluated after first and second line of treatment. 16 Pt. (group B) were evaluated after third and fourth line. Overall survival was calculated for patients included in each line of therapy using Kaplan Meier curve. Results: Group A: 13 men and 13 women, median age 57 years (37-81), 3 patients in stage IIIB and 23 stage IV, ECOG performance status=I for 20 Pt. and for Pt.=2, for 6Pt. Hystopathology: 25 adenocarcinomas and 2 large cell carcinoma; 12 smokers and 16 nonsmokers. First line consisted of: Paclitaxel + Carboplatin 11 (42%) Docetaxel + Carboplatin four (15%), Carboplatin + Vinorelbin 3 (12%), Pemetrexed + Carboplatin 2 (8%), Gem + Cys 2 (8) other 4 (15%). The median number of cycles in first line was 4 (2-4), in second line 7 (2-24). Overall survival in first line was 10 months. In group B: 12 men and 4 women, median age 62 years (31-80). 4 patients had stage IIIB and 12 stages IV, the histopathology was adenocarcinoma for all. ECOG performance status for all Pt. in first line of chemotherapy was I. First line chemotherapy was similar to group A except 3 Pt. treated in second line with Erlotinib and 2 cases treated with bevacizumab+paclitaxel and carboplatin. Median overall survival in this group was 6.5 months. Toxicity was no more than 2 on the WHO toxicity scale. Conclusion: In selected Pt. with NSCLC named those who responded to the first and second line chemotherapy or erlotinib, P can be administered in third and fourth line with survival benefits and acceptable toxicity. A large study is necessary to confirm the data obtained in this study. Once again highlighting the need of a marker of response to chemotherapy.

Keywords: Advanced Non-Small Cell Lung Cancer, chemotherapy, Third line chemotherapy

POSTER SESSION 2 – P2.03A: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/IMMUNOTHERAPY
CLINICAL TRIALS – TUESDAY, DECEMBER 6, 2016
P2.03A-067 THERAPY-RELATED LEUKEMIA AFTER LUNG CANCER CHEMOTHERAPY
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Keywords: Chemotherapy, Gemcitabine, Cisplatin, drug interaction

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Background: Therapy-related leukemia defined by the World health Organization 2008 classification scheme of hematolymphoid tumors including therapy-related acute myeloid neoplasms (t-AML), myelodysplastic syndrome (t-MDS). They occur as late complication of cytotoxic chemotherapy, radiation therapy and molecular target agents therapy against primary neoplasms. Recently, for lung cancer chemotherapy, new anti-cancer agent and molecular target agents are increased and more intensification chemotherapy performed. We report that we reviewed t-AML cases who survived from lung cancer and suffered t-AML. Methods: We intended for multiple neoplasms 339 cases including hematological malignancy. We reviewed 55 multiple neoplasms including the lung cancer. In 55 cases, second neoplasms that were t-AML cases were 4 cases, t-MDS case was 1 case. All patients were followed up until death or until December 2015. Survival was measured from the diagnosis of multiple cancer to time of death or last contact. We investigated cytogenetic abnormality, therapy, clinical outcome, prognosis, and cause of death. Results: In 5 cases, 4 cases were diagnosed t-AML, 1 case was t-MDS. 5 of cases were male and 1 female, primarily diagnosis were small cell carcinoma 2 cases, squamous carcinoma adenocarcinoma 3 cases. 1 case, One case(male case) was t-AML, he treated by all-trans retinoic acid and he reached complete response. T-M2 type, his treated by chemotherapy included daunorubicin and Ara-C(DC3-7), she did not achieve complete response. About prognosis, t-AML case, he lived 3 month after complete response, he died by lung cancer, t-AML cases, one female case, she lived 25 months after partial response, she died by t-AML relapse and refractory for salvage Ctx. Other 3 cases, 1 case death by t-MDS, 2 cases death by t-AML. Conclusion: As the number of lung cancer survivors increased due to improvement in chemotherapy, clinician must more take attention of therapy-related leukemia and myelodysplastic syndrome by previous treatments.

Keywords: chemotherapy, therapy-treated AML, therapy-related MDS

P2.03A-068 IMPACT OF PLATINUM/PEMETREXED VERSUS OTHER PLATINUM-BASED REGIMENS ON ADJUVANT CHEMOTHERAPY IN RESECTED ADENOCARCINOMA LUNG CANCER

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Background: Adjuvant chemotherapy improves the survival for completely resected non-small cell lung cancer (NSCLC) patients. Platinum/pemetrexed is known to be less toxicity, better compliance and longer survival in advanced non-squamous NSCLC, but the survival outcome compared with other regimens in adjuvant setting is still unknown. This report described the survival in adjuvant chemotherapy for lung adenocarcinoma with platinum/ pemetrexed versus other platinum-based doublets. Methods: 389 completely radical surgery lung adenocarcinoma patients who received adjuvant chemotherapy with platinum/pemetrexed regimen (Group A, n=143) and non-pemetrexed platinum-based regimens (Group B, n=246) were analyzed retrospectively. Primary end point was disease-free survival (DFS). Propensity score matching (PSM) allowed best matched pairs for platinum/pemetrexed versus other platinum-based doublets for comparison of survival and adverse events. Results: PSM created treatment groups for platinum/pemetrexed versus non-pemetrexed regimen (125 pairs), docetaxel and paclitaxel (107 pairs), gemcitabine (56 pairs), and vinorelbine (24 pairs)-contained doublets, respectively. Although DFS was not significantly different between Group A and B (P=0.1634)(Figure A), in 125 PSM pairs, DFS was considerably better in patients who received platinum/pemetrexed regimen (P=0.0079)(Figure B). From the subgroup analysis, Pemetrexed benefit is consistent across different subgroups, and especially among patients aged ≥65 was associated with the decision to use platinum/pemetrexed (HR=0.25, 95%CI 0.09-0.67, P=0.011). Furthermore, platinum/pemetrexed was associated with several significantly lower hematological and non-hematological AE rates, such as versus gemcitabine (Leukopenia: RR 0.51, p=0.001; Neutropenia: RR 0.688, p=0.002) and paclitaxel- and docetaxel-based chemotherapy (Leukopenia: RR 0.685, p=0.019; Neutropenia: RR 0.805, p=0.032).

Conclusion: Adjuvant chemotherapy with platinum/pemetrexed shows both better disease-free survival and less clinical toxicity than other non-pemetrexed based doublets in completely resected adenocarcinoma lung cancer.

Keywords: pemetrexed, disease free survival, lung adenocarcinoma, adjuvant chemotherapy

P2.03A-069 EFFECTIVENES OF ADJUVANT CARBOPLATIN-BASED CHEMOTHERAPY COMPARED TO CISPLATIN IN RESECTED NON-SMALL CELL LUNG CANCER

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Background: Cisplatin and vinorelbine given intravenously is a well-established adjuvant chemotherapy regimen after surgery for early NSCLC. However, few validated alternative exist when cisplatin is not indicated or tolerated. Carboplatin is frequently used in this setting. We evaluated the 5 years overall survival (OS), progression-free survival (PFS) and toxicity in patients treated for stage IB to IIIIB resected NSCLC receiving adjuvant carboplatin based chemotherapy compared to cisplatin in association with vinorelbine. Methods: Single-center retrospective study of patients having received adjuvant chemotherapy between January 2004 and December 2013 at the oncology clinic at Institut de Cardiologie et de Pneumologie de Québec (Canada). Three sub-groups were studied: cisplatin / vinorelbine (CISV), carboplatin / vinorelbine (CBV) and the substitution of cisplatin / vinorelbine for carboplatin / vinorelbine after carboplatin / vinorelbine during treatment. Results: A total of 127 patients were included in this study. The overall survival (OS) at 5 years and the median progression-free survival (PFS) did not differ significantly between groups. The 5 years OS is respectively 66 %, 55 % and 70 % (p=0.95). The PFS is respectively 50, 6 and 57, 3 months for the CISV and CISV/CBV groups and was not achieved for the CBV group (p = 0.80). No differences were noted between groups concerning grade 3 or 4 hematologic toxicity. Conclusion: The effectiveness and hematologic toxicity are comparable between cisplatin and carboplatin in the adjuvant treatment of resected non-small cell lung cancer. The results obtained corroborate the practice used at our oncology clinic. Nevertheless, more prospective studies would be needed to confirm these results.

Keywords: ADJUVANT, chemotherapy, Cisplatin, carboplatin
Background: Albumin-bound paclitaxel (nab-paclitaxel) has been demonstrated to improve outcomes with lesser neuropathy compared to that with paclitaxel in patients with advanced non-small cell lung cancer (NSCLC). However, the feasibility of adjuvant chemotherapy setting is still uncertain. This phase II trial assessed the feasibility of adjuvant chemotherapy with nab-paclitaxel and carboplatin in patients who underwent complete resection of pathological stage IB/II/IIIA NSCLC. Methods: Patients with completely resected pathological stage IB/II/IIIA NSCLC were recruited from July, 2013. Patients were administered adjuvant chemotherapy with 4 cycles of carboplatin (AUC 5) on day 1 and nab-paclitaxel (100 mg/m2) on days 1 and 8 every 3 weeks. The primary endpoint was the completion of 3 cycles of chemotherapy. The sample size was set at 30 patients, and the treatment was considered feasible if the 80% CI of the completion rate of 3 cycles of chemotherapy was > 60%, α=0.05 and β=0.2. Results: The study enrolled 30 patients including 2 pilot patients. The median relative dose intensities of modified weekly carboplatin and nab-paclitaxel were 80% and 70%, respectively. First two pilot patients were required dose reduction in conventional weekly carboplatin (AUC5) on day1 and nab-paclitaxel (100 mg/ m2) on days 1, 8 and 15 every 3 weeks, therefore we modified this setting. Among the treated patients, grade 3 adverse event listed neutropenia (60%) and thrombocytopenia (10%). Dose delays were observed in 20% of patients owing to neutropenia (85%). In this interim result analysis, all 10 patients completed 3 cycles of chemotherapy. Conversely, neuropathy did not develop in any patients. Neither febrile neutropenia nor treatment-related mortality was observed in this study. Conclusion: Based on the results, modified adjuvant chemotherapy with weekly nab-paclitaxel and carboplatin is feasible, with acceptable hematologic and non-hematologic toxicity, in patients who undergo complete resection of pathological stage IB/II/IIIA NSCLC.

Keywords: adjuvant chemotherapy, paclitaxel

P2.03A-070 A FEASIBILITY STUDY OF ADJUVANT CHEMOTHERAPY WITH MODIFIED WEEKLY NAB-PACLITAXEL AND CARBOPLATIN FOR COMPLETELY RESECTED NSCLC

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Background: The role of perioperative chemotherapy in completely resected NSCLC is controversial. This phase II trial evaluated the feasibility of modified weekly chemotherapy (MWCT) with nab-paclitaxel, carboplatin, and epirubicin. Methods: Patients with completely resected NSCLC who underwent curative surgery were eligible. The primary endpoint was the feasibility of 3 cycles of chemotherapy. The treatment was considered feasible if the 80% CI of the completion rate of 3 cycles of chemotherapy was > 60%, α=0.05, and β=0.2. Results: 27 patients were enrolled (group A: Modified weekly nab-paclitaxel, carboplatin, and epirubicin). The median number of cycles was 3. Dose delays were observed in 20% of patients owing to neutropenia (85%). In this interim result analysis, 10 patients completed 3 cycles of chemotherapy. Conclusion: Modified weekly nab-paclitaxel, carboplatin, and epirubicin is feasible in patients with completely resected stage I/II/IIIA NSCLC. The hematologic and nonhematologic toxicities of the regimen are acceptable.

Keywords: Adjuvant chemotherapy, nab-paclitaxel

P2.03A-071 ADJUVANT CHEMOTHERAPY FOLLOWING RESECTION OF NSCLC: AN AUDIT OF 5 YEARS OF PRACTICE AND OUTCOMES IN SOUTH WEST WALES

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Background: A number of meta-analyses have shown post-operative chemotherapy is beneficial following curative surgery for NSCLC, with the LACE meta-analysis demonstrating a 5 year survival improvement of 5.4%. NICE guidance states that cisplatin based combination chemotherapy should be offered to all patients of good PS with T1-3, N1-2, MD disease, and should be considered in T2-3 NO disease if > 4cm. The primary outcome of this audit was to review 5 years of practice; to assess adherence to guidelines in offering post-operative chemotherapy, and overall survival. Methods: Data was collected retrospectively from electronic records of patients who underwent surgery for lung cancer across Abertawe Bro Morganwg University Health Board and Hywel Dda Health Board between 2009 and 2014. Data collected included; demographics, date of diagnostic CT scan, date and type of surgery, histology, pathological stage, PET SUV max of primary tumour, date adjuvant chemotherapy started, regimen received, date of recurrence and overall survival. Spss software was used to collate results and statistical analysis. Results: Of the 281 patients, 241 had a histological diagnosis of NSCLC. Median age was 69 years. By stage; 31.9% IA, 40.3% IB, 9.2% IIa, 10.1% IIb, 7.5% IIIA, 0.4% IIIB, 0.4% IV. 88.8% underwent lobectomy, 4.9% excision, 0.4% pneumonectomy. 62.5% of patients with stage IIA, IIb or IIIA disease adjuvant chemotherapy (n=46/64), 70% of these received a cisplatin based combination (cisplatin/vinorelbine), 84% completed 6 cycles of treatment. 9.45% stage IA patients underwent chemotherapy which is not in accordance with guidance. The mean time from diagnostic CT to surgery was 109 days, and from surgery to post-operative chemotherapy 62 days. The one year overall survival (OS) was 89.6%, 80.1% and 82.6%, and the three year OS was 70.7%, 59% and 32.4%, for stage I, II and III respectively. 213 (88.4%) patients underwent PET scan with mean maximum SUV of 12.1 (range 1.0-76.3). There was no statistically significant relationship between SUV max and OS. Conclusion: Our data shows good compliance with national guidance in offering postoperative chemotherapy, and survival rates better than published UK survival data.

Keywords: postoperative, ADJUVANT, chemotherapy, outcomes
experimental group (15 cases): the Endostar (15 mg/m², intravenous infusion, d1-7) synchronization of WBRT (40 Gy/20 fractions/4 weeks); control group (15 cases): WBRT alone. Cerebral blood volume (CBV), blood flow (CBF) and mean perfusion time (MTT) and lymphocyte analysis were observed by magnetic resonance perfusion imaging before and 4 weeks after WBRT. Results: In experimental group, CBV and MTT at baseline were 582.12±161.42, 524.00±428.64 and 235.00±149.36. Four weeks after treatment, those perfusion values were 260.00±356.6, 336.00±480.82 and 509.00±44.34 respectively, which showed obvious decreasing trends compared with baseline data in CBF and CBV, while increased in MTT (Fig.1).

Figure 1: The measurement of MR perfusion imaging of brain.

Figure 2: Immune function related indicators. All the ten cases showed a partial response (PR) to therapy in experimental group, while in the control group the response rate was 40%. Endostar in combination with WBRT was generally well tolerated. Conclusion: Endostar combined with WBRT appears to be an efficacy and tolerable treatment of BM.

Keywords: whole brain radiation therapy, non-small cell lung cancer, Brain metastasis, Endostar

POSTER SESSION 2 – P2.03B: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/IMMUNOTHERAPY/IMMUNOTHERAPY BRAIN META – TUESDAY, DECEMBER 6, 2016

P2.03B-003 MUTATION PROFILE & HISTOLOGY ACCORDING TO ERS/ATC/IASCAL ASSOCIATED WITH IPFS TO WBI IN BM PATIENTS WITH RECENT ADENOCARCINOMA LUNG CANCER

Oscar Arrieta1, Enrique Caballe-Perez1, Laura-Alejandra Ramirez-Tirado1, Alberto Mejía-López1, Monika Blake Cerda1, Diana Flores-Estrada1, Omar Macedo-Pérez1, Andres-Felipe Cardona-Zorrilla1, Jaime De La Garza1
1Thoracic Oncology Unit and Laboratory of Personalized Medicine, National Cancer Institute, Mexico City/Mexico, 2Thoracic Oncology Unit and Laboratory of Mjersonalized Medicine, Instituto Nacional de Cancerología, Mexico City/Mexico, 3Departamento de Radiooncología, Instituto Nacional de Cancerología, Mexico City/Mexico, 4Unidad Funcional de Oncología Torácica Y Laboratorio de Medicina Personalizada, National Cancer Institute, Mexico City/Mexico, 5Clinical and Translational Oncology Group, Bogotá/Colombia

Background: Brain-metastases (BM) are a common metastatic site in non-small cell lung cancer (NSCLC). We studied the impact of genetic alterations (EGFR, ALK and KRAS) in relation to objective response rate (ORR), intracranial-progression-free survival (IPFS) and overall-survival (OS) after whole-brain irradiation (WBI) in patients at recently diagnosis with NSCLC and BM. Methods: From 2009-2015, 231 NSCLC patients with BM were reviewed for eligibility. Among them, 121 patients with recently diagnosis of NSCLC, were treated with WBI and have available genotyping status. Results: EGFR, KRAS, ALK and WT patients were found in 38.0%, 6.6%, 5.8% and 49.6%, respectively. Overall, ORR and disease control rate (DCR) were 62.0% and 76.8%, respectively. ORR for EGFR, KRAS, ALK and WT patients were 82.6%, 25.0%, 71.4% and 50.0%, respectively (p=0.001). Female gender (OR 2.22 [95% CI: 1.01 – 4.89] P=0.047) and EGFR were associated to better response to WBI (OR 5.67 [95% CI 2.0-15.8], P = 0.001). A high architectural histological grade was independently associated with resistance to WBI. Median IPFS was 9.06 months [95% CI 6.5 -11.4]. IPFS for EGFR, K-RAS,ALK and WT patients were 11.9, 4.6,12.5 and 6.6 months, respectively (P <0.0001). EGFR mutation status (HR 0.54 [95%CI 0.3-0.9], P = 0.030) was the only factor associated with higher IPFS in the multivariate Cox-regression analysis. Median OS was 16.6 months (95% CI11.6-22.6). OS for EGFR, ALK, KRAS and WT patients were 26.8, 13.5, 4.9 and 13.6 months, respectively (P <0.001). Intracranial OR was associated with a higher OS (HR 0.28 [95%CI 0.2-0.5], P < 0.001), while KRAS mutation positive status (HR 3.45 [95%CI 1.4-8.4], P = 0.006) was independently associated with worse OS.

A. Waterfall plot of the percentage of change from baseline in tumor size (bars) and the OS (dots) among patients by mutation status.

B. Waterfall plot of the percentage of change from baseline in tumor size (bars) and the IPFS (dots) among patients by mutation status.

C. Kaplan-Meier curves for the OS of the patients by mutations status.

D. Kaplan-Meier curves for the IPFS of the patients by mutations status.
Conclusion: EGFR mutation is an independent predictive factor for OR to WBI for BM in patients with NSCLC. KRAS mutation is an independent predictive factor for worse OS after BM.

Keywords: Intracranial response, Radiotherapy, NSCLC, brain metastases

P2.03B-004 FACTORS ASSOCIATED WITH BRAIN METASTASIS IN PATIENTS WITH LUNG ADENOCARCINOMA AFTER SURGICAL RESECTION

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Taipei Veterans General Hospital and National Yang-Ming University, Taiwan/Taiwan

Background: The aim of the study is to demonstrate the relationship between clinicopathological variables and brain metastasis in patients with resected lung adenocarcinoma. Methods: The clinicopathological characteristics of 748 patients of resected lung adenocarcinoma at Taipei Veterans General Hospital between 2004 and 2012 were retrospectively reviewed. Comprehensive histological subtyping was performed according to the percentage of each invasive histologic component. The prognostic value of clinicopathological variables for brain metastasis-free survival was demonstrated. Results: Among the 182 patients with distant metastasis, 93 (51.1%) patients developed central nervous system (CNS) metastasis, 118 (64.8%) had brain metastasis, 71 (39.0%) had bone metastasis, and 18 (8.9%) had liver metastasis during follow-up. Greater tumor size (HR, 1.276; 95% CI, 1.148 to 4.163; p = 0.017), stage II or III vs. stage I (HR, 2.469; 95% CI, 1.201 to 5.076; P = 0.014), angiolymphatic invasion (HR, 1.818; 95% CI, 1.037 to 3.189; P = 0.037), and micropapillary predominant (HR, 2.686; 95% CI, 1.270 to 5.683; P < 0.010) were significantly associated with more brain metastasis in multivariate analysis. Angiolymphatic invasion (HR, 2.632; 95% CI, 1.420 to 4.879; P = 0.002) and micropapillary predominant (HR, 2.186; 95% CI, 1.148 to 4.163; P = 0.017) were significant prognostic factors for worse brain metastasis-free survival in multivariate analysis. Conclusion: Angiolymphatic invasion and micropapillary predominant pattern are significantly associated with brain metastasis in patients with resected lung adenocarcinoma. This information is important for patient follow-up strategy and further study of the mechanisms leading to brain metastasis.

Keywords: brain metastasis, histology, adenocarcinoma, prognosis

P2.03B-005 CORRELATION BETWEEN PRIMARY TUMOR LOCATION AND BRAIN METASTASIS DEVELOPMENT OR PERITUMORAL BRAIN EDEMA IN LUNG CANCER

Katalin Fabjan1, Márton Gyulai2, József Furák1, Péter Varállay1, Mátyás Jäckel3, Krisztina Bogos2, Balazs Dome1, Judit Pápay1, József Timár1, Zoltán Szallas1, Judit Moldvay1
1Semmelweis University Department of Pulmonology, Budapest/Hungary, 2County Hospital of Pulmonology, Törökbálint/Hungary, 3Semmelweis University, IST Department of Pathology and Experimental Cancer Research, Budapest/Hungary

Background: It is often difficult to evaluate the status of EGFR mutation in non-small cell lung cancer (NSCLC) patients with brain metastases either from primary or metastatic lesions. Is it possible to ascertain the EGFR status and to guide the usefulness of TKI according to the MR imaging features of metastatic brain lesions in brain? Methods: Patients diagnosed with NSCLC from June 2014 through May 2015 were identified synchronously brain metastases based on enhanced magnetic resonance imaging (MRI). The variables of metastatic brain tumor included the numbers and the size of the brain lesions, the size of the associated peritumoral brain edema (PTBE) measured about EGFR mutation status. Results: Among 156 patients, 41 had the exon 19 deletion, 48 had the exon 21 L858R point mutation, and 67 had the wild-type EGFR. The exon 19 deletion group and exon 21 point mutation group had smaller peritumoral brain edema than did the wild-type group (P = 0.002 and P = 0.010, respectively). Different from the wild-type group, the exon 21 point mutation group showed more multiple brain tumors (P = 0.020). There was no significant difference about the size of the largest brain tumors in either exon 19 deletion group or exon 21 point mutation group when compared with the wild-type group (P = 0.077 and P = 0.051, respectively), but the metastatic brain lesions were inclined to smaller in EGFR mutation groups. Conclusion: Specific features of MRI in brain metastatic lesions were found in NSCLC with EGFR mutation, including smaller peritumoral brain edema and more lesions than did those with wild-type EGFR. Meanwhile, there was the trend that the size of the largest brain lesion was smaller in EGFR mutation groups. Accumulation of more knowledge was needed to depend on radiomics to make a quantifying analysis of EGFR mutation status.

Keywords: EGFR mutation, brain metastases, lung cancer

P2.03B-006 DISTINCT MR IMAGING FEATURES OF METASTATIC LESIONS IN BRAIN WITH NON-SMALL CELL LUNG CANCER ACCORDING TO EGFR MUTATION STATUS

Yan Cheng1, Xiaolong Fu1, Jun Liu1, Hongxuan Li1, Jing Chen1
1Radiation Oncology, Shanghai Chest Hospital, Shanghai, China

Background: The aim of this study is to evaluate the primary tumor location and brain metastasis development or peritumoral brain edema in lung cancer patients with resected lung adenocarcinoma. Methods: The clinicopathological characteristics of 748 patients of resected lung adenocarcinoma at Taipei Veterans General Hospital between 2004 and 2012 were retrospectively reviewed. Comprehensive histological subtyping was performed according to the percentage of each invasive histologic component. The prognostic value of clinicopathological variables for brain metastasis-free survival was demonstrated. Results: Among the 182 patients with distant metastasis, 93 (51.1%) patients developed central nervous system (CNS) metastasis, 118 (64.8%) had brain metastasis, 71 (39.0%) had bone metastasis, and 18 (8.9%) had liver metastasis during follow-up. Greater tumor size (HR, 1.276; 95% CI, 1.148 to 4.163; p = 0.017), stage II or III vs. stage I (HR, 2.469; 95% CI, 1.201 to 5.076; P = 0.014), angiolymphatic invasion (HR, 1.818; 95% CI, 1.037 to 3.189; P = 0.037), and micropapillary predominant (HR, 2.686; 95% CI, 1.270 to 5.683; P = 0.010) were significantly associated with more brain metastasis in multivariate analysis. Angiolymphatic invasion (HR, 2.632; 95% CI, 1.420 to 4.879; P = 0.002) and micropapillary predominant (HR, 2.186; 95% CI, 1.148 to 4.163; P = 0.017) were significant prognostic factors for worse brain metastasis-free survival in multivariate analysis. Conclusion: Angiolymphatic invasion and micropapillary predominant pattern are significantly associated with brain metastasis in patients with resected lung adenocarcinoma. This information is important for patient follow-up strategy and further study of the mechanisms leading to brain metastasis.

Keywords: brain metastasis, histology, adenocarcinoma, prognosis

P2.03B-007 PALLIATIVE WHOLE BRAIN RADIOTHERAPY IN ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC), THE UNIVERSITY COLLEGE LONDON HOSPITAL EXPERIENCE

Amy Ward, Hemal Ariyaratne, Dawn Carnell
University College London, London/United Kingdom

Background: Brain metastases occur in 30-40% of patients with Non-Small Cell Lung Cancer (NSCLC). Whole Brain Radiotherapy (WBRT) has been standard treatment in those with multiple metastases although this has been challenged by the Quartz trial. This suggested there was no advantage over supportive care in terms of survival (median 66 days in the RT arm) or quality of life. In our centre Quartz has divided opinions and practice. We thus decided to review our data of 163 patients who were treated with WBRT in the context of advanced NSCLC. Methods: Radiotherapy database information was used to identify patients receiving WBRT for metastatic NSCLC between 2007 and 2015. Patients with completely resected brain metastasis were excluded. Notes were reviewed retrospectively. Data were collected on demographics, performance status (PS), histology, disease status, further treatment following WBRT and survival. Results: 163 patients were identified of which 153 had complete follow up data to review. The demographics are
presented in the table below. The median survival across all patients was 104 days. Longer survival was seen in those with PS0/1 (median = 225 days) vs. PS3 (median = 44 days). Of the 19 patients surviving longer than 1 year, 95% were PS0/1. Of the 172 patients with brain metastases, 70% were PS0/1 vs. 3. None of them received further treatment following WBRT.

### PERFORMANCE STATUS

<table>
<thead>
<tr>
<th>DISEASE STATUS</th>
<th>Number</th>
<th>%</th>
<th>Median Survival (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain metastasis as 1st presentation of NSCLC</td>
<td>77</td>
<td>47%</td>
<td>146</td>
</tr>
<tr>
<td>Brain metastasis in known NSCLC</td>
<td>86</td>
<td>53%</td>
<td>85</td>
</tr>
<tr>
<td>Extracranial metastasis</td>
<td>125</td>
<td>78%</td>
<td>89</td>
</tr>
<tr>
<td>No Extracranial metastasis</td>
<td>35</td>
<td>22%</td>
<td>160</td>
</tr>
<tr>
<td>Further treatment following WBRT</td>
<td>55</td>
<td>36%</td>
<td>313</td>
</tr>
</tbody>
</table>

### OVERALL SURVIVAL

104 days

#### CONCLUSION

In our series survival was seen to be favorable when compared to the radiotherapy arm of Quatz. Performance status and the option for further treatment seemed to improve outcome. Whilst lacking QOL data and a supportive care control group, our data would suggest that for selected patients, especially those of good PS there remains a role for WBRT in NSCLC.

#### Keywords

Brain metastasis, WBRT, non-small cell lung cancer

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**POSTER SESSION 2 - P2.03B: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/ IMMUNOTHERAPY BRAIN META - TUESDAY, DECEMBER 6, 2016**

**P2.03B-008 THE IMPACT OF BRAIN METASTASES AND THEIR TREATMENT ON HEALTH UTILITY SCORES IN MOLECULAR SUBSETS OF LUNG CANCER PATIENTS**

Grainne O’Kane, Catherine Labbe, Susie Su, Brandon Tse, Vivian Tam, Tiffany Tse, Mark Doherty, Erin Stewart, Catherine Brown, Andrea Perez Cosio, Devalben Patel, Mindy Liang, Gurshuran Gill, Alexandra Rett, Yvonne Leung, Tse, Mark Doherty, Erin Stewart, Catherine Brown, Andrea Perez Cosio, Of LUNG CANCER PATIENTS

**HISTOLOGY**

- Adenocarcinoma EGFR WT
- Adenocarcinoma EGFR Mutant
- Adenocarcinoma ALK rearrangement
- Squamous cell Carcinoma
- Other Inc. NSCLC NOS

### PERFORMANCE STATUS

- PS0/1: 72, 44% (225 days)
- PS2: 56, 34% (80 days)
- PS3: 28, 17% (44 days)

### OVERALL SURVIVAL

104 days

**Background:** New therapies, particularly in advanced patients with EGFR-mutated and ALK-rearranged tumors, result in prolonged survival. Brain metastases and/or their treatment, may have a negative impact on health-related quality of life. Technological assessment of the cost-effectiveness of various treatments for brain metastases will benefit from measurements of health-related quality of life and health utility scores (HUS). This study evaluated the impact of brain metastases on HUS across multiple health status definitions based on the basis of disease stability, brain-specific therapies, and molecularly-defined subsets of NSCLC. Methods: A longitudinal cohort study at Princess Margaret Cancer Centre evaluated 1571 EQSD-3L derived HUS in 476 Stage IV lung cancer outpatients, from Dec, 2014 through May, 2016. EQSD (n=183), ALK+ (n=38), wild-type (WT) non-squamous (n=171), squamous (n=29), and small cell lung cancer (SCLC) (n=30). Patients were stratified according to presence or absence of brain metastases at the time of assessment; mean HUS (± standard error of the mean, SEM) by presence of brain metastases and various health states and disease subtypes were reported. For patients with repeated measures, only the earliest time point was analyzed. Results: 172 patients had brain metastases, median age 62, (range 32-86) years and 304 patients did not have brain metastases, median age 66 (29-90) years. Overall HUS was related to disease subtype but not presence of brain metastases: EGFR/ALK+ patients (0.78±0.02) or without brain metastases (0.79±0.01) versus WT/NSCLC with (0.74±0.02) and without brain metastases (0.73±0.01) (p=0.011 by subtype; p=0.10 by presence of brain metastases). However, symptomatic CNS disease (0.69±0.04) had lower HUS (versus asymptomatic disease (0.77±0.02)) (p=0.03). Patients achieving intracranial stability or response to treatment had significantly higher HUS (0.81±0.05) than patients with progressive CNS metastases (0.72±0.02) (p=0.03). Extra-cranial control also correlated with higher HUS (0.81±0.02 versus 0.69±0.03, p<0.0001). When local treatment for brain metastases was delivered within 6 months, HUS was lower (0.71±0.02 versus 0.82±0.02, p<0.0005). CNS disease treated only with systemic therapy or on no active therapy had mean HUS of 0.81±0.03, while patients treated only with stereotactic radiosurgery (SRS) had values of 0.80±0.04; there was a trend for lower HUS with whole brain radiation (WBRT) only (0.72±0.03) or WBRT+SRS (0.74±0.03) (p=0.11). Conclusion: Brain metastasis stability has significant impact on HUS in lung cancer patients. Treatment modalities of brain metastases may also impact HUS. Data collection is ongoing; updated HUS data including longitudinal assessments and multivariable analyses will be presented.

**Keywords:** brain metastases, health utility scores, NSCLC

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**P2.03B-009 BRAIN METASTASIS AND EPIDERMAL GROWTH FACTOR RECEPTOR MUTATIONS IN CAUCASIAN COUGS WITH LUNG ADENOCARCINOMA**

Katherina Sreter1, Suzana Kukulj2, Silvana Smojver-Jezek2, Ante Rebic2, Marina Serafovic3, Gordana Dripa2, Filip Popovic4, Bernard Budimir5, Sven Sestanik6, Marko Jakopovic2, Miloslav Samarcija2

1Department of Clinical Immunology, Pulmonology, and Rheumatology, University Hospital Centre “Sestre Milosrdnice”, Zagreb/Croatia, 2Department of Medical Oncology, Clinic for Respiratory Diseases “Jordanovac”, University Hospital Centre Zagreb, Zagreb/Croatia, 3Department of Cytology, Clinic for Respiratory Diseases “Jordanovac”, University Hospital Centre Zagreb, Zagreb/Croatia, 4University of Zagreb, School of Medicine, Zagreb/Croatia, 5Department of Pathology, University Hospital Centre Zagreb, School of Medicine, Zagreb/Croatia, 6Post-Intensive Care, Clinic for Respiratory Diseases “Jordanovac”, University Hospital Centre Zagreb, Zagreb/Croatia

**Background:** The brain is a common site of metastasis in non-small cell lung cancer (NSCLC). The aim of this study was two-fold: 1) to determine the incidence of brain metastasis (BM) in Caucasian lung adenocarcinoma patients with epidermal growth factor receptor (EGFR) mutations and 2) to evaluate the frequencies and potential relationship of the different EGFR mutations with BM. Methods: A retrospective cohort study was conducted at a Croatian tertiary hospital (Clinic for Respiratory Diseases “Jordanovac”) using data collected from medical records. Caucasian patients with primary NSCLC who were tested for EGFR mutation status between January 2014 and October 2015 were included. Results: Of 1040 NSCLC samples tested, 122 (11.7%) patients with lung adenocarcinoma harboured EGFR mutations; six EGFR positive (+) patients (four with BM) had repeat EGFR testing. The majority of EGFR mutant females were females (n=90, 77.6%), non-smokers (including never-smokers and former-smokers; n=95, 92.2%), diagnosed with advanced disease (stage III/IV) at first presentation (n=75, 68.8%), and median age at initial diagnosis of primary lung cancer was 65 years (35–90). Twenty-three (19.8%) of 116 EGFR+ patients were diagnosed with BM; for six EGFR+ patients, data about BM was missing. Most were 64 years of age or younger (n=54, 65.2%) at diagnosis of BM (median age 62, range 18 and 20) were found in two non-BM patients (2.2%). Conclusion: Larger long-term prospective studies to explore and confirm these results in BM+EGFR+ patients are warranted. In the era of precision oncology, molecular testing
Background: We aimed to investigate the feasibility of droplet digital PCR (ddPCR) for the detection of epidermal growth factor receptor (EGFR) mutations in circulating free DNA (cfDNA) from cerebrospinal fluid (CSF) and plasma of advanced Lung Adenocarcinoma (ADC) with brain metastases (BM). Methods: Fourteen advanced ADC patients with BM carrying activating EGFR mutations in tumour tissues were enrolled in this study, and their matched CSF and plasma samples were collected. EGFR mutations were detected by the Amplification Refractory Mutation System (ARMS) in tumour tissues. EGFR mutations, including 19del, L858R, and T790M were examined in cfDNA isolated from 2 milliliter CSF or plasma by ddPCR assay. The clinical response was assessed according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 guidelines. Overall survival (OS) and progression free survival (PFS) after the diagnosis of BM were also evaluated. Results: Out of 14 patients, eleven were females and three males aged from 34 to 74 years old (median age of 55 years old). In all of cases, CSF cytology were negative. In ddPCR assays, EGFR mutations were detected in CSF of three patients (21.4%; one of 19del and two of L858R), and in plasma of six patients (42.9%; one of 19del, one of L858R, one of T790M, two of L858R&T790M, and one of 19del&T790M). All EGFR T790M mutations were found during or after EGFR-TKIs treatments. The three patients with activating EGFR mutations in CSF achieved partial response (PR) of BM after treated with combination of WBRT and EGFR-TKis. The median OS and PFS after the diagnosis of BM were 18.0 months and 9.0 months, respectively.

Keywords: Cerebrospinal fluid, EGFR mutation, brain metastases, lung adenocarcinoma

<table>
<thead>
<tr>
<th>Patient</th>
<th>Tissue EGFR</th>
<th>CSF EGFR</th>
<th>Plasma EGFR</th>
<th>Systematic Treatment</th>
<th>BM Treatment</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>19del</td>
<td>WT</td>
<td>T790M</td>
<td>Gefitinib +Chemotherapy</td>
<td>WBR + Gamma knife</td>
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<tr>
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<td>Gefitinib +Chemotherapy</td>
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<tr>
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<td>L858R</td>
<td>Gefitinib +Chemotherapy</td>
<td>WBR</td>
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<td>Gefitinib +Chemotherapy</td>
<td>WBR</td>
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<td>Chemotherapy</td>
<td>WBR</td>
</tr>
</tbody>
</table>

Conclusion: It was feasible to test EGFR mutation in CSF. CSF may serve as liquid biopsy of advanced ADC with BM by enabling measurement of cfDNA within CSF to characterize EGFR mutations.

Keywords: EGFR mutations may further clarify the pathogenesis of lung cancer-associated BM.

Key: precision medicine, brain metastases, non-small cell lung cancer, Epidermal growth factor receptor mutations.
of 37 days and accumulation in tumors with permeable vasculature. This phase II trial evaluated the CNS activity of etirinotecan pegol in patients with lung cancer and refractory brain metastases. Methods: Patients with lung cancer and brain metastases were eligible who had received prior systemic therapy and prior brain-directed neurosurgery, radiation/radiosurgery, or refused whole brain radiotherapy (WBRT). Measurable brain metastases were defined as one >= 10 mm; or one 5-9 mm with others >= 3 mm, totaling >= 30 mm. Eritinotecan pegol was administered at 145 mg/m2 IV every 3 weeks. Response (modified RECIST 1.1) was assessed with brain MRI and systemic CT every 6 weeks. The primary endpoint was a 25% or greater 12-week CNS disease control rate (CNS-DCR; defined as unconfirmed response or stable disease with systemic non-progression) in a non-small cell lung cancer (NSCLC) cohort. Another exploratory cohort enrolled small cell lung cancer (SCLC) patients. Results: In the NSCLC cohort, twelve patients were enrolled, all with adenocarcinoma. Genomic alterations included six (50%) with EGFR mutation, and one each with HER2, KRAS, ROS1, and NTRAS. Patients received a median of 2.5 prior systemic treatments. Two (17%) patients had prior neurosurgery, ten patients (83%) had irradiation - 3 WBRT, 9 radiosurgery. Common neurological adverse events (AE) were headache in 41.7% (each 16/31 (51.6%) patients), and blurred vision (22%) (22/105 (21%)). One patient died after developing diarrhea and dehydration. CNS responses lasting 24, 8, and 6 weeks were observed in 25% (3/12) - all EGFR mutation positive. The 6-week CNS-DCR was 50% (6/12), but 12-week CNS-DCR was 17% (2/12). Median progression-free survival was 11.6 weeks (95% CI 5.3-11.7) and median overall survival from study entry was 29.6 weeks (95% CI 22.3-38.2).

In the SCLC cohort, two patients were enrolled. One patient with prior PCI had CNS response at 5 weeks but died of neutropenic infection; one who refused prior WBRT had CNS progression at 6 weeks. Conclusion: Radiographic responses of brain metastases were observed in patients following administration of etirinotecan pegol, but the study did not meet the primary endpoint because the 12-week CNS-DCR was 17%. Further study of etirinotecan pegol is ongoing in patients with breast cancer and brain metastases. Keywords: Brain metastasis, chemotherapy, non small cell lung cancer
P2.03B-015 EFFICACY OF THE IRREVERSIBLE ERBB FAMILY BLOCKER AFATINIB IN TREATMENT OF AN INTRACEREBRAL NON-SMALL CELL LUNG CANCER IN MICE
Lucheng Zhu1, Shriong Zhang2, Yanping Jiang1, Jing Zhang1, Yasi Xu1, Bing Xia1, Shenglin Ma1
1Department of Radiation Oncology, Hangzhou First People’s Hospital, Nanjing Medical University, Hangzhou, China, 2Center for Translational Medicine, Hangzhou First People’s Hospital, Nanjing Medical University, Hangzhou, China

Background: The prognosis of brain metastases (BM) from lung cancer is extremely poor. Some studies showed patients with BM responded well to afatinib, while little was known on detail mechanism. This study aimed to evaluate the efficacy of afatinib in treating BM, whether BM could actively penetrate brain-blood barrier (BBB) and hit its target. Methods: Tumor burden was evaluated weekly after administration of afatinib and vehicle, and pharmacokinetic and pharmacodynamics characteristics were measured in both normal mice and BM model mice. Results: Administration of 15mg/kg afatinib inhibited brain tumor growth by 80% in the normal mice with an inhibitory rate (TGI) of 78.9% and 90.2% on day 4 and 14, respectively. 30mg/kg afatinib exhibited the tumor regression on day 7 and 14 with TGI of 124.7% and 105%. The plasma concentration was 91.4±3.1 μM/L at 0.5h after afatinib administration, reached the peak (417.7±119.5 μM/L) at 1h, and still be detected at 2h. The EC50 was 0.84 μM. A good correlation (R2=0.732) between plasma and CSF concentrations was demonstrated. Immunohistochemistry showed the signal of pEGFR was reduced by 90% at 1h after administration of 30mg/kg afatinib. A positive correlation between afatinib concentrations in CSF and pEGFR modulation was observed. Conclusion: Afatinib could penetrate into BBB contributing to brain tumor response. The exposure in CSF correlated with that in plasma, which was correlated with modulations of pEGFR in the tumor tissues. Our findings provide implication of potential application of afatinib in NSCLC patients with brain metastases.

Keywords: Brain metastasis, afatinib, non-small cell lung cancer, tyrosine kinase inhibitor

P2.03B-016 TESETAVATINIB IN NSCLC PATIENTS WITH EGF PROTEIN ACTIVATING MUTATIONS AND BRAIN METASTASES (BM) OR LEPTOMENIGEAL METASTASES (LM)
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Background: Tesetavatib is a potent reversible EGFR inhibitor with strong preclinical evidence of brain penetration: brain:plasma ratios of 1-4 and brain:meninges ratios of 10-15 in rodents (AACR 2015 Abstract 2590). Tesetavatib is previously shown have growth inhibition in brain with tumor growth inhibitory rate (TGI) of 79.8% and 90.2% on day 7 and 14, respectively. 30mg/kg afatinib exhibited the tumor regression on day 7 and 14 with TGI of 124.7% and 105%. The plasma concentration was 91.4±3.1 μM/L at 0.5h after afatinib administration, reached the peak (417.7±119.5 μM/L) at 1h, and still be detected at 2h. The EC50 was 0.84 μM. A good correlation (R2=0.732) between plasma and CSF concentrations was demonstrated. Immunohistochemistry showed the signal of pEGFR was reduced by 90% at 1h after administration of 30mg/kg afatinib. A positive correlation between afatinib concentrations in CSF and pEGFR modulation was observed. Conclusion: Afatinib could penetrate into BBB contributing to brain tumor response. The exposure in CSF correlated with that in plasma, which was correlated with modulations of pEGFR in the tumor tissues. Our findings provide implication of potential application of afatinib in NSCLC patients with brain metastases.

Keywords: Brain metastasis, afatinib, non-small cell lung cancer, tyrosine kinase inhibitor

P2.03B-017 DIFFERENCES OF CENTRAL NERVE SYSTEM METASTASIS DURING GEFITINIB OR ERLOTINIB THERAPY IN PATIENTS WITH EGF-MUTATED LUNG ADENOCARCINOMA
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Background: A few reports have suggested a difference in the incidences of new metastasis to the central nervous system (CNS) during gefitinib and erlotinib therapy. However, a direct comparison of these two therapies has not yet been reported. We planned a retrospective study to investigate the incidences of CNS metastasis progression (new CNS metastasis or progression of existing CNS metastasis) during gefitinib and erlotinib therapy in patients with non-small cell lung cancer (NSCLC) harboring EGF mutation. Methods: We retrospectively analyzed the incidences of CNS metastasis progression and the outcomes of NSCLC patients harboring EGF mutation who received gefitinib or erlotinib as a first-line EGFR-TKI treatment at the National Cancer Center Hospital between 2008 and 2014. Results: A total of 175 patients were analyzed; 148 patients had received gefitinib, and 27 had received erlotinib. The median (range) ages were 64.5 (32-81) years and 62.0 (27-68) years, respectively, exon 19 deletion/L858R point mutations were present in 84/64 (56.7%/43.3%) cases in the gefitinib group and 21/6 (77.8%/22.2%) cases in the erlotinib group, respectively. The status of CNS metastasis before EGFR-TKI therapy was negative/positive in 105/43 (71.0%/29.0%) cases in the gefitinib group and 21/6 (77.8%/22.2%) cases in the erlotinib group, respectively. The incidence of CNS metastasis progression in the gefitinib group tended to be higher than that in the erlotinib group (P = 0.051). In patients without CNS metastasis before EGFR-TKI therapy, the incidence of new CNS metastasis during EGFR-TKI treatment was significantly higher in the gefitinib group than in the erlotinib group (24.7% vs. 4.8%, P = 0.04). The progression-free survival (PFS) and overall survival (OS) of patients with CNS metastasis were both shorter than those of the patients who presented without CNS progression (median PFS. 9.5 vs. 12.6 months, P = 0.034; median OS. 23.8 vs. 34.1 months, P = 0.002). Fifty-six patients underwent re-biopsy after the failure of EGFR-TKI therapy, but no difference in the incidences of EGFR T790M mutation was seen between patients with and those without CNS metastasis progression (40.0% for patients without CNS progression vs. 63.6% for patients with CNS metastasis progression, P = 0.19). Conclusion: The incidence of the progression of CNS metastasis during gefitinib therapy was higher than that during erlotinib therapy. In addition, the difference in this incidence was more remarkable among patients who had not developed CNS metastasis prior to the start of EGFR-TKI therapy.

Keywords: EGF-mutated NSCLC, Erlotinib, CNS Metastasis, gefitinib

P2.03B-018 CLINICAL DATA FROM THE REAL WORLD: EFFICACY OF CRIZOTINIB IN CHINESE PATIENTS WITH ADVANCED ALK+ NON-SMALL CELL LUNG CANCER AND BRAIN METASTASES
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Background: Brain metastasis in NSCLC patients is often considered as a poor predictive indicator for overall survival (OS). Some studies showed that patients with brain metastasis had longer OS than those without. The mechanism of this phenomenon is still not understood. This study aimed to identify the clinical factors that influence the outcome of patients with NSCLC with brain metastasis. Methods: We retrospectively analyzed the clinical data of a total of 377 patients with NSCLC with brain metastasis from the first 7 patients in this ongoing clinical trial indicate that tesevatinib has clinical activity in the CNS in EGFR mutant disease manifesting as BM or LM in patients previously treated with erlotinib, gefitinib, or afatinib. An additional cohort of 20 treatment-naïve patients who have initial presentation with brain metastases is being added.

Keywords: EGFR Inhibitor, Brain Metastases, Leptomeningeal Metastases

P2.03B-019 CLINICAL DATA FROM THE REAL WORLD: EFFICACY OF CRIZOTINIB IN CHINESE PATIENTS WITH ADVANCED ALK+ NON-SMALL CELL LUNG CANCER AND BRAIN METASTASES
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Background: Brain metastasis in NSCLC patients is often considered as a
terminal stage of advanced disease. Crizotinib is a small-molecule tyrosine kinase inhibitor (TKI) for ALK-rearranged NSCLC patients that can improve systemic outcomes. Herein, a retrospective analysis of Crizotinib was performed in advanced ALK-rearranged NSCLC patients with brain metastases, to explore how Crizotinib affects the control of brain metastases and the overall prognosis in Chinese population in the real world. Methods: Advanced NSCLC patients with brain metastases who underwent Crizotinib treatment at the Cancer Hospital of the Chinese Academy of Medical Sciences between April 2013 and April 2015 were included. ALK translocation was determined by FISH, Ventana IHC test or RT-PCR. Brain metastases were diagnosed by CT or MRI. Results: A total of 34 patients were enrolled, of whom 20 patients had baseline brain metastases at the initiation of Crizotinib treatment. For patients with baseline metastases, overall survival (OS) after brain metastases was significantly longer, compared with those developing brain metastases during Crizotinib treatment (median OS, not reached vs. 10.3 months, p = 0.001). Among all the patients treated with chemotherapy at the first line, OS after brain metastases with baseline brain metastases was significantly superior than those without (p = 0.023). Whereas, patients receiving Crizotinib at the first line with baseline brain metastases didn’t demonstrate such superior (p = 0.089). Among patients who developed brain metastases during Crizotinib treatment, for those receiving chemotherapy at the first line, the result was not significant by the cut-off date, time to brain metastases was longer, compared with patients receiving Crizotinib at the first line (median time to brain metastases, 17.1 months vs. 10.5 months, p = 0.072).

Conclusion: Chinese ALK-rearranged NSCLC patients with baseline brain metastases may benefit more from Crizotinib than those developing brain metastases during Crizotinib treatment.

Keywords: non-small cell lung cancer, Brain metastasis, crizotinib, Real world

P2.03B-019 COMPARISON OF THE EFFICACY OF FIRST-GENERATION EGFR-TKIS IN BRAIN METASTASIS
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Background: Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) are more effective in patients with advanced non-small-cell lung cancer (NSCLC) with EGFR mutations, compared with standard chemotherapy. In Japan, gefitinib, erlotinib, afatinib, and osimertinib have been approved so far. However, data comparing the efficacies of different EGFR-TKIs, especially in brain metastasis, are lacking. Methods: EGFR-TKI-naïve patients with recurrent or stage IB/IV NSCLC with EGFR mutations, excluding resistance mutations, were enrolled in this study. We retrospectively analyzed the time to progression of brain metastasis in patients who received either gefitinib or erlotinib using the Kaplan-Meier method with the log-rank test. Results: Seventy-eight EGFR-TKI-naïve patients received either gefitinib (n = 55) or erlotinib (n = 22) from April 2010 to April 2016 in our hospital. During EGFR-TKI treatment, brain metastasis progression was observed in 10 of the 56 patients (17.9%) in the gefitinib group and in 1 of the 22 patients (4.5%) in the erlotinib group. Prior to EGFR-TKI treatment, 15 patients in the gefitinib group and 12 in the erlotinib group had brain metastasis. Among these patients, brain metastasis progression was observed in 7/15 (46.7%) in the gefitinib group and 0/12 (0%) in the erlotinib group. Although event (brain metastasis progression)-free survival was marginally better in the erlotinib group, erlotinib significantly reduced brain metastasis progression in patients who had brain metastasis prior to EGFR-TKI treatment compared with gefitinib (P = 0.011, Figure).

Conclusion: Although this was a retrospective analysis involving a small sample size, erlotinib is potentially more promising than is gefitinib for brain metastasis in patients with EGFR-mutant NSCLC, especially those with brain metastasis prior to EGFR-TKI treatment.

Keywords: metastasis, brain, EGFR-TKI, NSCLC

P2.03B-020 EGFR EXON 19 DELETION MUTATION PATIENTS OBTAIN OPTIMAL SURVIVAL IN ICOTINIB TREATED NON–SMALL-CELL LUNG CANCER PATIENT WITH BRAIN METASTASES
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Background: Lung cancer is characterized by the highest incidence of solid tumor-related brain metastases. This is also one of the reasons why it can cause significant mortality. Molecular targeted therapy plays a major role in the management of brain metastases in lung cancer, which has become the novel methods for treatment of lung cancer with brain metastases. Our study aims to explore the efficacy of the EGFR targeted treatments in NSCLC brain metastases, specially according to EGFR mutation sub-types.

Methods: We collected 116 patients with NSCLC brain metastases who underwent EGFR-TKIs therapy from 2011-2015 of Zhejiang cancer hospital. The data were analyzed to get progression-free survival for intracranial disease(MPFSI), median progression-free survival for extracranial disease(MPFS), median overall survival (MOS), which were evaluated by Kaplan-Meier and multivariate analysis were performed by Cox model.

Results: The overall response rate for 116 patients with icotinib treatment was 61%. No increase in neurotoxicity was detected. The overall response rate was significant higher with EGFR exon 19 deletion mutation than with EGFR exon 21 mutation, other type EGFR mutations or EGFR-wildtype (P<0.05). MPFSI, MPFSE and MOS was also significantly longer with EGFR exon 19 deletion mutation than with EGFR exon 21 mutation, other type EGFR mutations or EGFR-wildtype (68% VS 42%). MPFSI, MPFSE and MOS was also significantly longer with EGFR exon 19 deletion mutation than with EGFR exon 21 mutation, other type EGFR mutations or EGFR-wildtype (P<0.05).

Conclusion: Icotinib was well tolerated and efficacious in patients with brain metastases who were poor responders to standard EGFR-TKIs.

Keywords: EGFR mutation, TKI, Brain metastasis, non-small cell lung cancer
Abstracts

POSTER SESSION 2 – P2.03b: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/IMMUNOTHERAPY
Biomarkers –
TUESDAY, DECEMBER 6, 2016

P2.03B-021 SCREENING FOR MAJOR ONCOGENE ALTERATIONS IN ADENOSQUAMOUS LUNG CARCINOMA USING PCR COUPLED WITH NEXT-GENERATION AND SANGER SEQUENCING METHODS

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Background: Despite progress in personalized lung adenocarcinoma treatment, development of efficacious molecular targeted therapies for adenosquamous cell carcinoma (ASC) of the lung has made little progress because of limited knowledge concerning gene mutation status and the rarity of this type of tumor. Methods: We examined the frequency of EGFR, K-Ras, B-Raf, PIK3CA, DDR2, ALK, and PDGFRα gene mutation using NGS, PCR, and Sanger sequencing methods in ASC samples. Macrodisssection or laser microdissection was performed in 37 cases to separate adenomatous and squamous components of ASC for further sequencing. Fifty-six patients who underwent operations in Peking Union Medical College Hospital between January 2010 and December 2014 were enrolled in the study. Results: The overall mutation rate was 64.29%, including 55.36%, 7.14%, and 1.79% for EGFR, K-Ras, and B-Raf mutations, respectively. PIK3CA mutation was detected in three cases; all involved coexisting EGFR mutations. Of the 37 cases, 34 were convergent in two components, while three showed EGFR mutations in the glandular components and three showed PIK3CA mutations in the squamous components. With respect to EGFR mutations, the number of young female patients, nonsmokers, and those with positive pleural invasion was higher in the mutation-positive group than that in the mutation-negative. K-Ras mutation was significantly associated with smoking. Overall survival in the different EGFR mutation groups differed significantly.

Conclusion: The frequency and clinicopathological characteristics of EGFR- and KRAS-mutated adenosquamous lung carcinoma were similar to that noted in Asian adenocarcinomas patients. The high convergence mutation rate in both adenomatous and squamous components suggests monoclonality in ASC.

Keywords: K-RAS, adenosquamous lung carcinoma, next generation sequencing method, EGFR

POSTER SESSION 2 – P2.03b: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/IMMUNOTHERAPY
Biomarkers –
TUESDAY, DECEMBER 6, 2016

P2.03B-022 OUTCOME IN MOLECULARLY DEFINED NSCLC WITHIN THE NOWEL NETWORK: THE INFLUENCE OF SEQUENTIAL 2ND AND 3RD GENERATION TKI IN EGFR MT+ AND ALK+ PTS

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Background: Available clinical research data shows that early mutation testing for patients with NSCLC stage IV could lead to an effective choice of therapy for patients with a proved mutation. Targeted therapies achieve a better quality of life, a higher PFS and ORR and in some cases increased OS. The aim of the study was therefore to systematically analyze retrospective data from three cancer centers in the north of Germany. The study compares these three cancer centers in reference to the test rate and the therapeutic success of targeted therapy. Methods: 1383 patients from the three cancer centers diagnosed with non-small lung cancer stage IV (UICC 7) were examined. Methods for the detection of mutations included Sanger Sequencing, hybridization based COBAS testing as well as hybrid cage next generation sequencing. Clinical characteristics including smoking status were available for more than 92% of the patients. Results: 880 consecutive patients from the three cancer centers were studied for the presence of tumor mutations, especially for EGFR and ALK mutations. The overall mutation testing rate was 63.6% (880/1383). EGFR mutations were found in 18.4% (86/467)/ 13.1% (38/289)/ 11.3% (14/124) in the Pius-Hospital, Bremen-Ost. Conclusion: The frequency and clinicopathological characteristics of EGFR- and KRAS-mutated adenosquamous lung carcinoma were similar to that noted in Asian adenocarcinomas patients. The high convergence mutation rate in both adenomatous and squamous components suggests monoclonality in ASC.
Cancer Center, Houston/TX/United States of America, TP53 frequency) were one somatic alteration detected. The most commonly observed SNVs (> 5% in the 2016 LUSC TCGA dataset. Results: 426 patients (92.2%) had at least one SNV detected by Guardant 360. Somatic alterations were compared with those in TCGA (CNAs), indels, and fusions. The median time between diagnosis and ctDNA testing was 238 days. Somatic alterations were compared with those in TCGA (Spearman r = 0.93) but were generally lower in our cohort (Table 1). Several of our most frequently observed CNAs were increased by over-expressing miR-330-3p using a lentivirus carrying a miR-330-3p cassette. In addition, MET exon 14 skipping (1.3%), EGFR exon 19 deletion (1.5%), EML4-ALK fusion (0.7%) were detected. These alterations have rarely been reported in LUSC. Conclusions: Patterns of SNVs and CNAs in LUSC obtained by ctDNA profiling are largely consistent with those from TCGA tissue profiling, reported in LUSC. Conclusion: Patterns of SNVs and CNAs in LUSC obtained by ctDNA profiling are largely consistent with those from TCGA tissue profiling, reported in LUSC. Conclusion: Patterns of SNVs and CNAs in LUSC obtained by ctDNA profiling are largely consistent with those from TCGA tissue profiling, reported in LUSC. Conclusion: Patterns of SNVs and CNAs in LUSC obtained by ctDNA profiling are largely consistent with those from TCGA tissue profiling, reported in LUSC. Conclusion: Patterns of SNVs and CNAs in LUSC obtained by ctDNA profiling are largely consistent with those from TCGA tissue profiling, reported in LUSC. Conclusion: Patterns of SNVs and CNAs in LUSC obtained by ctDNA profiling are largely consistent with those from TCGA tissue profiling, reported in LUSC. Conclusion: Patterns of SNVs and CNAs in LUSC obtained by ctDNA profiling are largely consistent with those from TCGA tissue profiling, reported in LUSC. Conclusion: Patterns of SNVs and CNAs in LUSC obtained by ctDNA profiling are largely consistent with those from TCGA tissue profiling, reported in LUSC. Conclusion: Patterns of SNVs and CNAs in LUSC obtained by ctDNA profiling are largely consistent with those from TCGA tissue profiling, reported in LUSC. Conclusion: Patterns of SNVs and CNAs in LUSC obtained by ctDNA profiling are largely consistent with those from TCGA tissue profiling, reported in LUSC. Conclusion: Patterns of SNVs and CNAs in LUSC obtained by ctDNA profiling are largely consistent with those from TCGA tissue profiling, reported in LUSC. Conclusion: Patterns of SNVs and CNAs in LUSC obtained by ctDNA profiling are largely consistent with those from TCGA tissue profiling, reported in LUSC. Conclusion: Patterns of SNVs and CNAs in LUSC obtained by ctDNA profiling are largely consistent with those from TCGA tissue profiling, reported in LUSC. Conclusion: Patterns of SNVs and CNAs in LUSC obtained by ctDNA profiling are largely consistent with those from TCGA tissue profiling, reported in LUSC. Conclusion: Patterns of SNVs and CNAs in LUSC obtained by ctDNA profiling are largely consistent with those from TCGA tissue profiling, reported in LUSC. Conclusion: Patterns of SNVs and CNAs in LUSC obtained by ctDNA profiling are largely consistent with those from TCGA tissue profiling, reported in LUSC. Conclusion: Patterns of SNVs and CNAs in LUSC obtained by ctDNA profiling are largely consistent with those from TCGA tissue profiling, reported in LUSC. Conclusion: Patterns of SNVs and CNAs in LUSC obtained by ctDNA profiling are largely consistent with those from TCGA tissue profiling, reported in LUSC. Table 1: Frequency of Significant SNVs and Tested CNAs (LUSC-associated CNAs in bold: NR = Not Reported)
sequence of miR-330-3p, and decreased by knockdown of miR-330-3p. In nude mice receiving subcutaneous A549 and HCC27 cell inoculation, tumor growth were significantly faster in mice receiving A549 and HCC27 cell permanently expressing exogenous miR-330-3p, and slower in cells permanently expressing an anti-miR-330-3p sequence. The mice receiving cancer cells stably expressing exogenous miR-330-3p injection directly into the brain almost developed multiple metastatic foci, while developed a smaller orthotopic tumor in mice receiving injection of cells expressing an anti-miR-330-3p sequence. GRIA3 was identified as a direct target of miR-330-3p using luciferase reporter assays. Real-time PCR and Western blot confirmed that miR-330-3p downregulated GRIA3 expression. MEK inhibition suggested that GRIA3 was regulated by miR-330-3p via MAPK/MEK/ERK signaling pathway. Conclusion: These results support the oncogenic role of miR-330-3p in NSCLC brain metastasis, providing a rationale for miRNA-targeted therapeutic strategies. Keywords: MAPK/MEK/ERK signaling pathway, Brain metastasis, microRNA-330-3p, non-small cell lung cancer

P2.03B-025 MUTATION PROFILE AND HISTOLOGY SUBTYPE ACCORDING TO IASLC/ERS/ATC AS RISK FACTORS FOR BRAIN METASTASES IN LUNG ADENOCARCINOMA
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Background: Brain metastases (BM) are common among patients with adenocarcinoma, affecting treatment response, quality of life and overall survival (OS). We examine the impact of the main histological pattern and the genetic alterations in EGFR and ALK on the incidence of BM in patients with advanced non-small cell lung cancer (NSCLC). Methods: From January 2004 through December 2016 the medical records of 991 patients with NSCLC were reviewed for eligibility, among them 711 had adenocarcinoma histology. We describe the factors associated with the overall incidence of BM as well as the incidence of BM stratified on the histological grade pattern according to the ERS/ATC/IASLC classification (lepidic vs acinar + papilar vs micropapilar + solid). Results: Among 711 patients, 53% were female, 47.1% were less than 60 years-old at the time of diagnosis, exposure to tobacco, wood-smoke and asbestos were found in 52.0%, 40.5% and 13.8%, respectively. Seventy-six percent had a good performance status, and nearly sixty percent (59.8%) had oligometastatic disease. Most of the patients had a stage IV disease at the time of diagnosis (79.3%). Regarding histological grade classification, male patients were more likely to have a poorly differentiated adenocarcinoma in comparison with women (61.2% vs. 51.2%, p=0.027), as well as ever-smokers compared with non-smokers (61.4% vs. 49.9%). Likewise, patients harboring an ALK rearrangement were more likely to have a highly- or moderately differentiated adenocarcinoma (100% vs. 43.6%, p=0.008). A total of 122 patients (17.1%) had a brain metastasis at diagnosis and 37.4% had baseline carcinomogenicric levels above 20 pg/ml. By Kaplan-Meier method 6.45% and 12.10% of patients developed BM at 12 and 24 months. The factors associated with a high incidence of BM were: female gender (40.9% vs. 34.4%, p=0.035), age ≤ 60 years (44.4% vs. 32.1%, p<0.001), EGFR activating mutation (53.9% vs. 39.3%, p=0.001), advanced metastatic disease (IIIB vs IV 42.8% vs. 20.3%, p<0.0001), serological carcinoembryonic level >20 pg/ml (47.2% vs. 32.8%, p<0.0001). Finally, brain metastases were more likely to be found among patients with moderate and poorly differentiated adenocarcinomas in comparison with highly differentiated adenocarcinomas (54.2, and 48.1% vs. 7.7%, p=0.050). In the multivariate analysis EGFR (HR:0.63,95%CI:0.44-0.92, p=0.017) and highly differentiated adenocarcinomas EGFR (HR:1.59,95%CI:1.03-2.44, p=0.034) were found to be independent factors for the development of brain metastases. Advanced adenocarcinoma histological-architectural- grade differentiation according to ERS/ATC/IASLC classification was found to be a predictive factor for development of BM like other previously described clinically characteristics (e.g. gender, age, EGFR activating mutations and carcinomogenicric-antigen). Keywords: risk factors, brain metastases, NSCLC, histologic architectural grade

P2.03B-026 NEXT-GENERATION SEQUENCING FOR MOLECULAR DIAGNOSIS OF TUMOUR SPECIMENS FROM PATIENTS WITH ADVANCED LUNG ADENOCARCINOMA
María Gabriela Fernandes1, José Costa1, Joana Reis2, Conceição Moura1, Vanessa Santos3, Henrique Queiroga1, Adriana Magalhães1, António Morais1, José Machado3, Venceslau Hespanhol1
1Respirology, Centro Hospitalar São João, Porto/Portugal, 2Respirology, Hospital do Cruzeiro, Guimarães/Portugal, 3Pathology, Centro Hospitalar São João, Porto/Portugal
Background: Next-generation sequencing in lung adenocarcinoma implies the detection of specific genetic alterations predictive of response to agents targeting specific pathways. Next Generation Sequencing provides simultaneous analysis of hundreds of genes in samples with low DNA quantity with a fast, sensitive technology, even in the presence of low frequency alleles. Methods: In this study, the enrichment strategy used was the Ion Ampliseq Colon and Lung panel for tumour biopsies. All amplified products were used to prepare libraries and sequenced using the Ion PGM or 55x system. The QuantStudio 3D Digital PCR System was used to confirm selected results. 92 patients with advanced lung adenocarcinoma previously tested for EGFR mutation by PCR and for ALK by FISH were included. Significant genetic alterations obtained by NGS were described and compared with those identified by standard techniques. Results: NGS was applied to 52 diagnostic samples, corresponding to 63 (68.5%) wild type (WT) patients, 21 (22.8%) with EGFR mutations and 8 (8.7%) with ALK-EML4 translocation. The Ion Torrent PGM confirmed the presence of the EGFR mutation in 20 (95.2%) patients and detected a new case with p.L858R. Among patients classified as WT, 18 had a KRAS mutation, 3 BRAF V600E and 1 STK11; among EGFR patients, 2 had a KRAS mutation. Other significant concurrent genetic alterations were found: 2 patients with EGFR and PIK3CA mutations, 2 with EGFR and KRAS and sporadic cases with STK11 and TP53. Only 40 patients remained classified as WT (42.5%). Conclusion: NGS is useful for detection of actionable mutations in small tumour biopsies and cytology specimens of lung adenocarcinoma. It allows the identification of more candidates to targeted therapies and the detection of concurrent mutations that can impact prognosis and treatment efficacy. Keywords: lung adenocarcinoma, mutations, tumour samples, next generation sequencing

P2.03B-027 CIRCULATING FREE DNA (CFDNA) ANALYSIS FROM PATIENTS WITH ADVANCED LUNG ADENOCARCINOMA
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1Respirology, Centro Hospitalar São João, Porto/Portugal, 2Respirology, Hospital do Cruzeiro, Guimarães/Portugal, 3Pathology, Centro Hospitalar São João, Porto/Portugal
Background: Circulating tumour free DNA (cfDNA) is a noninvasive assessment that can be used as an alternative method for gene mutations detection in lung cancer patients and for real time therapeutic monitoring. Detection and quantification of such mutations is difficult and next generation sequencing (NGS) is a promising technology. Concordance between tumour tissue DNA (tDNA) and plasma cfDNA need to be studied and changes in cfDNA correlated with clinical evolution. Methods: Ion Ampliseq Colon and Lung panel was used for tissue biopsies and the new Oncomine Lung cfDNA assay for cfDNA samples. All amplified products were used to prepare libraries and sequenced using the Ion PGM or 55x system. Selected results were confirmed with the QuantStudio 3D Digital PCR. Plasma cfDNA collected at the diagnosis and during disease’s evolution of patients with advanced adenocarcinoma was analysed. cfDNA mutations were compared with tDNA. Results: 56 patients were included. In the tumour samples 24 activating EGFR mutations, 16 KRAS, 3 BRAF V600E, 3 TP53, 1 STK11 and 1 PIK3CA were identified. In all patients, the tDNA was classified as “wild type” (WT). Tumour derived genetic alterations could be identified in cfDNA with allelic frequencies as low as 0.01%. Among the 48 alterations detected on tDNA, 39 (81.3%) were found in cfDNA. Plasma detection failed in 6 EGFR and 3 KRAS. In 13 EGFR patients, concurrent alterations not identified in the tumour were detected: 1 combination with EGFR p.Glu746_Ala750del, 2 with T790M and 1 with ALK p.I1171N. A KRAS mutation was identified in 1 WT patient. cfDNA
Abstracts

POSTER SESSION 2 – P2.03B: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/IMMUNOTHERAPY BIOMARKERS – TUESDAY, DECEMBER 6, 2016

P2.03B-028 IMPROVED OVERALL SURVIVAL FOLLOWING IMPLEMENTATION OF NGS IN ROUTINE DIAGNOSTICS OF ADVANCED LUNG CANCER IN GERMANY: RESULTS OF THE NGM

Anna Kostenko1, Sebastian Michels1, Jana Fassunke1, Lucia Nogova2, Sabine Merkelbach-Bruse1, Matthias Scheffler1, Vanessa Brandes1, Rieke Fischer1, Andreas Scheel1, Florian Kron1, Merle Schueller1, Frank Ueckeroth1, Reinhard Buettern1, Jörg Wolf2

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Background: Pulmonary adenoid cystic carcinoma (PACC) is one of the rare malignancies, that primary from glandular tissues of lung. Currently, the theoretical foundation for the precision therapy of PACC. Methods: 8 PACC patients who received surgical resection between January 2013 to December 2015 were enrolled. The tumor tissues from different locations and blood samples were collected. The oncoseq1 panel by Illumina platform, which utilizing probe hybridization to gathering 287 exon regions and 22 intron regions, were used to detect the gene mutation status of PACC. And the embryonal system mutations were filtered by contrasting the gene mutation status of the leukocytes. The tumor heterogeneity was revealed by comparing the gene mutation status in different areas of the same PACC, and the phylogenetic relationships were analyzed to disclose the evolving and developing progression of PACC. Results: There were 69 gene mutations together among 8 patients including 29 samples. Each patient has 8-6 mutations averagely. The high-frequency mutations were PAK3-D119E, FBXW7-D119E, TET2-T418I, KATEA-E796A, and MET-R1005Q. However, the common mutations in other NSCLC, like EGFR, KRAS, ALK, etc., weren’t happened in this group of PACC. In this study, the spatial heterogeneity was discovered in PACC, not only in the mutation site, but also in the mutant abundance. Moreover, the phylogenetic relationships revealed that the clonal evolution and development existed in PACC. Conclusion: The status of genomic alterations in PACC was different from the other non-small cell lung cancer (NSCLC). PACC showed obvious spatial heterogeneity and clonal evolution.

Keywords: next-generation sequencing, Heterogeneity, driver gene, pulmonary adenoid cystic carcinoma

POSTER SESSION 2 – P2.03B: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/IMMUNOTHERAPY BIOMARKERS – TUESDAY, DECEMBER 6, 2016

P2.03B-030 RETROSPECTIVE REVIEW CLINICAL USE OF A CFDNA BLOOD TEST FOR IDENTIFICATION OF TARGETABLE MOLECULAR ALTERATIONS IN PATIENTS WITH LUNG CANCER

Hai Tran1, Jianjun Zhang1, Marya Vasquez1, Frank Fossella2, George Simon3, Anne Tsao4, Don Lynn Gibbons4, Yasir Elamim4, Kimberly Banks4, Richard Lanman1, Vassiliki Papadimitrakopoulou4, John Heymach5

1Thoracic & Head and Neck Medical Oncology, University of Texas M.D. Anderson Cancer Center, Houston/TX/United States of America, 2Guardant Health, Inc, Redwood City, CA/United States of America

Background: The availability of tumor genomic information from simple, minimally invasive blood collection may lead to significant impact in patient(pt) care. We report a retrospective review the clinical utility of a CLIA-certified cell-free DNA (cfDNA) next generation sequencing (NGS) blood test in our pts with lung cancers. Methods: From April 2015 to May 2016, blood samples from 250 consecutive pts were collected and sent for molecular profiling at a CLIA-certified lab (Guardant360, Guardant Health, Redwood City, CA) using cfDNA NGS with a panel of 70 cancer-related genes (PLOS One, 10(10), 2015). Results: 254 Guardant360 tests were completed in 250 pts (144/106/10); histology: adenocarcinoma(200), squamous(7), sarcomatoid(5), small cell(6) and others(34). Rationale for blood tests: addition to tissue analysis(39%), histology: adenocarcinoma(200), squamous(7), sarcomatoid(5), small cell(6) and others(34). Rationale for blood tests: addition to tissue analysis(39%), alternative to tissue biopsy(25%), treatment evaluation/resistant(18%), insufficient tissue(11%), no documentation(7%). Based on Guardant360 results, 77 pts samples (30.3%) demonstrated targetable alterations with FDA-approved agents; concordance with at least 1 genomic alteration (targetable with FDA-approved agent) from paired tissue analysis in 21pts; and in another 29 pts, new genomic alterations provided evaluation for potential change in therapies pts: EGFR T790M (n=21), EML4-ALK fusion(n=4), MET exon 14 Skipping (3), EGFR ex9del(n=2), EGFR L858R(n=2), other targets(n=6). Significantly, detection of EGFR T790M in cfDNA lead to change in therapy for osimertinib 19 cases and eligibility to clinical studies in 2 cases with alterations in KIF5B-RET and NOTCH1, respectively. Additional clinical outcomes are pending and will be updated. Conclusion: Molecular testing of cfDNA is a simple, minimally invasive test. It has utility to obviate a repeat invasive tissue biopsy when the initial tissue sample is not available or inadequate for molecular analysis. It is particularly useful in the long-term management of patients at progression for detection of emergent resistance-associated molecular alterations; such as EGFR T790M.

Keywords: lung cancer, cfDNA, ctDNA, molecular alterations

POSTER SESSION 2 – P2.03B: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/IMMUNOTHERAPY BIOMARKERS – TUESDAY, DECEMBER 6, 2016

P2.03B-029 ANALYSIS OF GENOMIC ALTERATIONS AND HETEROGENEITY IN PULMONARY ADENOID CYSTIC CARCINOMA BY NEXT-GENERATION SEQUENCING

Min Li, Bingrong Zhao, Pengbo Deng, Liming Cao, Huaping Yang, Qihua Gu, Chengping Hu

Department of Respiratory Medicine, Xiangya Hospital, Central South University, Changsha/China

Background: Pulmonary adenoid cystic carcinoma (PACC) is one of the rare malignancies, that primary from glandular tissues of lung. Currently, the treatment of PACC relies on surgery and local radiotherapy. However the therapy for advanced PACC patients is limited. A larger number of studies demonstrated that advanced PACC patients obtained little benefit from chemotherapy. Moreover, only a few case reports revealed PACC patients were appropriate for target therapy. Using high-flux and high-resolution techniques to detect the genomic alterations of PACC could provide theoretical foundation for the precision therapy of PACC. Methods: 8 PACC patients who received surgical resection between January 2013 to December 2015 were enrolled. The tumor tissues from different locations and blood samples were collected. The oncoseq1 panel by Illumina platform, which utilizing probe hybridization to gathering 287 exon regions and 22 intron regions, were used to detect the gene mutation status of PACC. And the embryonal system mutations were filtered by contrasting the gene mutation status of the leukocytes. The tumor heterogeneity was revealed by comparing the gene mutation status in different areas of the same PACC, and the phylogenetic relationships were analyzed to disclose the evolving and developing progression of PACC. Results: There were 69 gene mutations together among 8 patients including 29 samples. Each patient has 8-6 mutations averagely. The high-frequency mutations were PAK3-D119E, FBXW7-D119E, TET2-T418I, KATEA-E796A, and MET-R1005Q. However, the common mutations in other NSCLC, like EGFR, KRAS, ALK, etc., weren’t happened in this group of PACC. In this study, the spatial heterogeneity was discovered in PACC, not only in the mutation site, but also in the mutant abundance. Moreover, the phylogenetic relationships revealed that the clonal evolution and development existed in PACC. Conclusion: The status of genomic alterations in PACC was different from the other non-small cell lung cancer (NSCLC). PACC showed obvious spatial heterogeneity and clonal evolution.

Keywords: next-generation sequencing, Heterogeneity, driver gene, pulmonary adenoid cystic carcinoma

POSTER SESSION 2 – P2.03B: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/IMMUNOTHERAPY BIOMARKERS – TUESDAY, DECEMBER 6, 2016

P2.038-029 ANALYSIS OF GENOMIC ALTERATIONS AND HETEROGENEITY IN PULMONARY ADENOID CYSTIC CARCINOMA BY NEXT-GENERATION SEQUENCING

Min Li, Bingrong Zhao, Pengbo Deng, Liming Cao, Huaping Yang, Qihua Gu, Chengping Hu

Department of Respiratory Medicine, Xiangya Hospital, Central South University, Changsha/China

Background: Pulmonary adenoid cystic carcinoma (PACC) is one of the rare malignancies, that primary from glandular tissues of lung. Currently, the treatment of PACC relies on surgery and local radiotherapy. However the longitudinal variations are being studied and will be updated. Conclusion: Profiling cfDNA with Ion NSG technology is feasible, allowing the detection of molecular alterations associated with targeted therapy or valuable for disease monitoring. cfDNA has a good correlation with tumour DNA alterations, representing a true “liquid biopsy”. The application of NGS to tumour and plasma samples hold a large spectrum of clinical potentialities.

Keywords: mutations, lung cancer, cfDNA, next generation sequencing
**P2.03B-031 IMPACT OF PD-L1 STATUS ON CLINICAL RESPONSE IN SELECT-1: SELUMETINIB + DOXETAXEL IN KRAS ADVANCED NSCLC**

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¹Dan-Farber Cancer Institute, Boston/MA/United States of America, ²Department of Thoracic Oncology, Netherlands Cancer Institute, Amsterdam/Netherlands, ³Multidisciplinary Oncology and Therapeutic Innovations Department, Aix Marseille University, Marseille/France, ⁴Department of Medical Oncology, Hospital University Malaga General, Malaga/Spain, ⁵Pulmonary Department, Toulouse University Hospital, Toulouse/France, ⁶Division of Medical Oncology, Santa Maria Della Misericordia Hospital, Perugia/Italy, ⁷Department of Medicine, Pavlov Medical University, St. Petersburg/Russian Federation, ⁸Manchester University and the Christie NHS Foundation Trust, Manchester/United Kingdom, ⁹Department of Internal Medicine, Center for Integrated Oncology, University Hospital of Cologne, Cologne/Germany, ¹⁰Medical Oncology Department, University Hospital Ramon Y Cajal, Madrid/Spain, ¹¹Astrazeneca, Cambridge/United Kingdom, ¹²Department for Clinical and Pre-Clinical Trials, Petrov Research Institute of Oncology, St. Petersburg/Russian Federation, ¹³Astrazeneca, Macclesfield/United Kingdom, ¹⁴Astrazeneca, Herfordshire/United Kingdom, ¹⁵Astrazeneca, Gaithersburg/MD/United States of America

**Background:** Anti-PD-1/PD-L1 immunotherapy has delivered clinical benefit for patients with NSCLC, and PD-L1 has emerged as a predictive biomarker. In the Phase III SELECT-1 trial (NCT01939392), selumetinib (AZD6244, ARY-124886), an oral, potent and selective, allosteric MEK1/2 inhibitor with a short half-life, plus second-line docetaxel did not provide clinical benefit for patients with KRAS-mutant (KRASm) NSCLC compared with placebo plus docetaxel (PBO+DOC). Although no incremental benefit was observed, it is important to evaluate biomarkers, such as PD-L1, to understand more about the biology of patients with KRASm NSCLC. Methods: In total, 510 patients with a prospectively, centrally confirmed KRAS mutation (KRASm) NSCLC were randomized 1:1 to selumetinib 75 mg BID, plus docetaxel 75 mg/m² q21d (SEL+DOC), or PBO+DOC. Evaluations included progression-free survival (PFS) by investigator assessment (RECIST 1.1; primary endpoint), and overall survival (OS). Association of tumour PD-L1 status with clinical responses was assessed as an exploratory objective. PD-L1 status was centrally determined using the PD-L1 IHC 28-8 pharmDx test (Dako) for all patients with sufficient tumour sample. Samples with a pre-specified cut-off of ≥5% tumour cell staining were considered PD-L1 positive. Results: In total, 510 patients with a prospectively, centrally confirmed KRAS mutation (cobas® KRAS Mutation Test, Roche Molecular Systems) were randomized 1:1 to selumetinib 75 mg BID, plus docetaxel 75 mg/m² q21d (SEL+DOC), or PBO+DOC. Evaluations included progression-free survival (PFS) by investigator assessment (RECIST 1.1; primary endpoint), and overall survival (OS). Association of tumour PD-L1 status with clinical responses was assessed as an exploratory objective. PD-L1 status was centrally determined using the PD-L1 IHC 28-8 pharmDx test (Dako) for all patients with sufficient tumour sample. Samples with a pre-specified cut-off of ≥5% tumour cell staining were considered PD-L1 positive. Results: Selumetinib plus docetaxel did not improve PFS or OS compared with placebo plus docetaxel. PD-L1 subgroup analysis of PFS and OS is presented below.

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Events (%) in SEL+DOC group</th>
<th>Events (%) in PBO+DOC group</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PD-L1&lt;5%</td>
<td>94/112 (84%)</td>
<td>101/112 (90%)</td>
<td>0.89 (0.67, 1.18)</td>
</tr>
<tr>
<td>PD-L1≥5%</td>
<td>65/79 (82%)</td>
<td>71/82 (87%)</td>
<td>0.70 (0.50, 0.99)</td>
</tr>
<tr>
<td>PD-L1 unknown</td>
<td>59/63 (94%)</td>
<td>57/62 (92%)</td>
<td>1.24 (0.86, 1.79)</td>
</tr>
<tr>
<td>OS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PD-L1&lt;5%</td>
<td>73/112 (65%)</td>
<td>74/112 (66%)</td>
<td>0.94 (0.68, 1.30)</td>
</tr>
<tr>
<td>PD-L1≥5%</td>
<td>55/79 (70%)</td>
<td>58/82 (71%)</td>
<td>0.89 (0.61, 1.28)</td>
</tr>
<tr>
<td>PD-L1 unknown</td>
<td>48/63 (76%)</td>
<td>38/62 (61%)</td>
<td>1.57 (1.02, 2.41)</td>
</tr>
</tbody>
</table>

**Conclusion:** Prevalence of PD-L1 positive status in this KRAsm cohort was similar to that reported for a pan-NSCLC cohort (Borgheai, NEJM 2015). No significant PFS or OS differences were observed between treatments in either PD-L1 positive or negative tumours. Additional biomarker analyses are planned for different KRAS codon mutations, and LKB1 and TP53 status.

Keywords: non-small cell lung cancer (NSCLC), phase III, KRAS, PD-L1

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**P2.03B-032 THE PECULIAR CHANGING PATTERN OF SERUM NSE ACTS AS AN INDICATOR OF TRANSFORMATION FROM ADENOCARCINOMA TO SCLC**

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**Background:** Cytophenotypic transformation from adenocarcinoma to SCLC raises much attention as a mechanism of drug resistance in NSCLC patients treated with EGFR-TKI therapy. However, there’s no noninvasive way to predict and monitor the occurrence of cell transformation.

**Methods:** We collected 362 cases of transformation from adenocarcinoma to SCLC to analyze the relationship among cancer development, tumor cell transformation and specific serum tumor marker of SCLC (NSE). The associations among the tumor medications, therapeutic effect and serum NSE were analyzed by chi-square test and Kaplan-Meier survival analysis was conducted by log-rank analysis in adenocarcinoma patients. Results: All 362 adenocarcinoma patients were collected from 2013 to 2015 in Shanghai Pulmonary Hospital and accepted EGFR mutation test. 79 patients accepted the repeat biopsy and 4 patients showed the cytophentypic transformation. In the cytophenotypic transformation cases, NSE was normal at first and increased remarkably during the treatment. The peculiar rising pattern of serum NSE matched the SCLC pathological confirmation in repeat biopsy. Then we further found that in 362 cases, 66 (18.2%) patients experienced the peculiar rising pattern of serum NSE. Notably, this kind of NSE changing pattern is associated with drug resistance (p=0.026), but has no relationship with EGFR mutation or targeted therapy. What’s more, the peculiar rising pattern of serum NSE during the first-line treatment led to a shortened PFS of the second-line treatment (p=0.042).

**Conclusion:** Cytophenotypic transformation from adenocarcinoma to SCLC develops no matter the EGFR mutation positive or not, targeted therapy taken or not. For adenocarcinoma patients, serum tumor markers, especially NSE, need highly attention in clinical practice. A repeat biopsy is strongly recommended when adenocarcinoma patients’ NSE level shows the peculiar rising pattern. Notably, this kind of NSE changing pattern matched the SCLC pathological confirmation in repeat biopsy. A repeat biopsy is strongly recommended when adenocarcinoma patients’ NSE level shows the peculiar rising pattern. Notably, this kind of NSE changing pattern matched the SCLC pathological confirmation in repeat biopsy.

Keywords: small cell lung cancer, Cytophentypic transformation, Serum NSE, Adenocarcinoma
Background: Personalized medicine significantly increases survival of lung adenocarcinoma patients. Currently, existing diagnostic guidelines include only EGFR and ALK testing, although other oncogenic drivers can be detected and targeted as well. Massive parallel sequencing (MPS) detects a wider spectrum of actionable genomic alterations (GAs) compared to regular molecular diagnostic procedures. Studies on the influence of hybrid capture-based (HC-based) MPS on therapeutic strategy are limited. In this study, we explored its impact on therapy management and clinical outcomes. Methods: A retrospective cohort of patients who were diagnosed with advanced stage lung cancer, and performed HC-based MPS between 11/2011 and 10/2015. Two platforms of HC-based MPS were included: a tissue based assay, and a blood based assay of circulating free DNA (cfDNA, “liquid biopsy”) for tissue-exhausted cases. Demographic and clinico-pathologic characteristics, treatments, and outcome data were collected and analyzed. Results: One hundred and one patients were analyzed in this study: median age, 63 years; 53% females; 45% never smokers; 85% with adenocarcinoma, 19/101 patients were analyzed in this study: median age, 63 years; 53% females; 45% never smokers; 85% with adenocarcinoma, 19/101 patients were analyzed in this study: median age, 63 years; 53% females; 45% never smokers; 85% with adenocarcinoma, 19/101 patients were analyzed in this study: median age, 63 years; 53% females; 45% never smokers; 85% with adenocarcinoma, 19/101 patients were analyzed in this study: median age, 63 years; 53% females; 45% never smokers; 85% with adenocarcinoma. Currently, existing diagnostic guidelines include only EGFR and ALK testing, although other oncogenic drivers can be detected and targeted as well. Results: One hundred and one patients were analyzed in this study: median age, 63 years; 53% females; 45% never smokers; 85% with adenocarcinoma, 19/101 patients were analyzed in this study: median age, 63 years; 53% females; 45% never smokers; 85% with adenocarcinoma, 19/101 patients were analyzed in this study: median age, 63 years; 53% females; 45% never smokers; 85% with adenocarcinoma, 19/101 patients were analyzed in this study: median age, 63 years; 53% females; 45% never smokers; 85% with adenocarcinoma, 19/101 patients were analyzed in this study: median age, 63 years; 53% females; 45% never smokers; 85% with adenocarcinoma, 19/101 patients were analyzed in this study: median age, 63 years; 53% females; 45% never smokers; 85% with adenocarcinoma.

Keywords: massive parallel sequencing, Driver Mutations, Targeted therapy, Immunotherapy

POSTER SESSION 2 – P2.03B: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/ IMMUNOTHERAPY BIOMARKERS – TUESDAY, DECEMBER 6, 2016

P2.03B-034 CLINICAL RELEVANT ONCOGENIC DRIVERS IN ADVANCED ADENOCARCINOMA DISCLOSES NEW THERAPEUTIC TARGETS IN NEGATIVE EGFR/ALK/KRAS PATIENTS

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Background: The mutation profile in the brazilian population with advanced lung adenocarcinoma remains largely unexplored and also their relationship to many other genes. Next Generation Sequencing (NGS) allows higher sensitivity and multiplexing for several genes for translational research Methods: 80 lung adenocarcinoma patients were collected. DNA concentration and quality was determined by qubit2.0 fluorometer and Agilent2100 bioanalyzer. Genomic libraries were constructed using the TruSeq® Custom Amplicon v1.5 comprising 764 amplicons of 38 genes on the illumina-Miseq® sequencing platform. Results: The 7362 genetic mutation were observed with 78% of single-nuclotide variants (SNVs) and 22% insertions and deletions. The majority of the SNVs were located in inter-genic regions or introns. EGFR were mutated in 21% of patients with 19 (57%) of mean expression. The most frequent EGFR mutation was exon 19 deletion, followed by L858R amino acid substitution in exon 21. KRAS was mutated in 26 (41%) of patients, ALK rearrangement was detected in 6 patients (4%). The stop gained mutation was present in PIK3CA, TP53, AXL, EGFR, RAB25, CDH1, CD276 and TGFBI. The AXL. The AXL receptor tyrosine kinase gene showed 11 missense-mutations, of which 7 are considered possibly damaging (PolyPhen)/deleterious(SIFT)(74/79) and 4 introns(SNVs/48/80). CD44 showed 50 variants, however most of them have an undetermined significance. The clustering analysis demonstrated that a select group of AXL-related gene alterations were highlighted (Fig 1). Conclusion: The results suggest that genomic variants in lung adenocarcinoma tissues are complex and show that NGS is an effective way to detect novel mutations in lung cancer. 58% of patients wild type by standard testing for EGFR/KRAS/ALK have genomic changes identifiable by CGP that suggest benefit from targeted therapy. The AXL and CD44 genes remain a relatively unexplored target, thus we intend to increase the available data for the true translational potential of target AXL and CD44 therapy in lung cancer. CGP used when standard molecular testing for adenocarcinoma is negative can reveal additional avenues of benefit from targeted therapy.

Keywords: non small cell lung cancer, advanced lung cancer, mutations, next generation sequencing
P2.03B-035 EGF FISH AS POTENTIAL PREDICTOR OF NECITUMUMAB BENEFIT WITH CHEMOTHERAPY IN SQUAMOUS NSCLC: SUBGROUP ANALYSES FROM SQUIRE
Carlo Genova1, Manileila Varella-Garcia2, Christopher Rivard1, Mark Socinski3, Rebecca Hosp3, Alain J. Amador4, Raffael Kurek2, Javad Shahidi1, Luz Pac-Ares5, Nick Thatcher6, Fred R. Hirsch7
1Lung Cancer Unit, IRCCS AOU San Martino - 1st, Genova, Italy, 2Medical Oncology, University of Colorado School of Medicine, Aurora/CO/United States of America, 3University of Colorado, Aurora/CO/United States of America, 4Executive Offices, 117th Floor, Florida Hospital Cancer Institute, Orlando/FL/United States of America, 5Oncology, Eli Lilly and Company, Indianapolis/IN/United States of America, 6Eli Lilly and Company, Indianapolis/IN/United States of America, 7Gps Medical and Benefit Risk Management, Lilly Deutschland GmbH, Deutschland, Germany 8Eli Lilly and Company Bridgewater, Bridgewater/NJ/United States of America, 9University Hospital Virgen Del Rocio, Seville/Spain, 10The Christie Hospital, Manchester/United Kingdom, 11University of Colorado Cancer Center, Aurora/CO/United States of America

Background: Necitumumab (Neci) is a monoclonal antibody directed against the human epidermal growth factor receptor (EGFR). In the SQUIRE trial (NCT00981058), the addition of Neci to gemcitabine plus cisplatin (Gem-Cis) in squamous cell lung cancer resulted in a significant advantage in progression-free survival (PFS) and each sample was analyzed using the Colorado EGFR mutation panel to assess the relationship between targetable mutations and survival outcomes.

Methods: Suitable specimens from SQUIRE patients underwent FISH analysis. Probe hybridization was performed in a central laboratory and each sample was analyzed using the Colorado EGFR scoring criteria. High polysomy was defined as ≥50% of cells with ≥4 EGFR copies or ≥230% copy number with ≥15 EGFR copies. The correlation of polysomy status and clinical outcomes was assessed. Results: FISH analysis was available for 557 patients (out of 1093); 208 patients (37.3%) were FISH+.

Table: HIGH POLYSOMY

<table>
<thead>
<tr>
<th>Median OS in months (95% CI)</th>
<th>Hazard ratio within subgroup (interaction model)</th>
<th>Interaction p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.55 (2.79-8.34)</td>
<td>0.70 (0.50-0.99) p = 0.044</td>
<td>0.49 (0.21-0.93) p = 0.033</td>
</tr>
<tr>
<td>6.08 (5.59-7.59)</td>
<td>0.77 (0.55-1.08) p &lt; 0.001</td>
<td>0.189</td>
</tr>
<tr>
<td>12.58 (11.04-16.00)</td>
<td>14.78 (10.02-31.51)</td>
<td></td>
</tr>
</tbody>
</table>

Conclusion: The OS benefit from the addition of Neci to Gem-Cis appeared to be more pronounced in the subset of patients with high polysomy (≥50%) compared with other EGFR FISH subgroups (p = 0.033 vs 0.980).

Keywords: Necitumumab, EGFR, FISH, Squamous cell carcinoma

P2.03B-036 ANALYSIS OF POTENTIALLY TARGETABLE MUTATIONS IN 821 PATIENTS WITH SQUAMOUSCELL LUNG CANCER UNDERGOING ROUTINE NGS-BASED MOLECULAR DIAGNOSTICS
Sophia Koleck1, Carsten Schapers1, Matthias Scheffler1, Michaela Ihls2, Anna Kostenko3, Svetlana Michels4, Rieke Fischer5, Lucia Negrova6, Monika Serke7, Britta Kaminsky6, Ulrich Gerigk8, Josef Benedikter9, Tim Brummendorf10, Joachim Ficker10, Wolfgang Kruis10, Joachim Lorenz10, Clemens Chulte11, Susanne Schulze-Olden11, Sabine Merkelbach-Bruse12, Frank Ueckeroth12, Reinhard Bütter13, Jürgen Wolf14
1University Hospital Cologne, Department for Internal Medicine, Lung Cancer Group Cologne, Cologne/Germany, 2University Hospital Cologne, Lung Cancer Group Cologne, Cologne/Germany, 3Department of Pathology University Hospital of Cologne, Cologne/Germany, 4Department I of Internal Medicine, University Hospital of Cologne, Cologne/Germany, 5Lungenklinik Hemer, Hemer/Germany, 6Hospital Bethanien, Solingen/Germany, 7Mälzer Krankenhaus Seliger Gerhard, Bonn/Germany, 8City Hospital Munich, Munich/Germany, 9Ruw Aachen, Aachen/Germany, 10Pulmonology and Thoracic Oncology, Klinikum Nuernberg & Paracelsus Universitat Nuernberg, Nuernberg/Germany, 11Evangelic Hospital Cologne Kalk, Cologne/Germany, 12Hospital Ludenscheid, Ludenscheid/Germany, 13Practice for Hematology and Oncology, Dortmund/Germany, 14Florence Nightingale Hospital, Dusseldorf/Germany, 15Institute of Pathology, University Hospital of Cologne, Cologne/Germany

Background: Molecular multiplex diagnostics is increasingly integrated now in routine diagnostics of lung adenocarcinoma (LAD). Although targetable aberrations are predominantly found in LAD, they have also been reported in squamouscell lung cancer (SCLC). We here present results of routine molecular multiplex diagnostics of advanced stage SCLC obtained within the German Network Genomic Medicine (NGM) and compare them with results reported previously in early stage SCLC in The Cancer Genome Atlas (TCGA) LUSC cohort. Methods: Tumor biopsies of 821 patients consecutively diagnosed within NGM were analyzed with next-generation parallel sequencing (NGS). The panel consisted of 102 amplicons and 14 genes: KRAS, PIK3CA, BRAF, EGFR, ERBB2, NRAS, DDR2, TP53, ALK, CNTRNB1, MET, AKTI, PTEN and MAP2K1. In subsets of patients, fluorescence-in-situ hybridization (FISH) was performed for amplification detection of FGFR1 and MET. We queried the TCGA dataset with respect to the panel used and compared the findings. For NGS patients, therapy and outcome are also included also activating targetable mutations (i.e., EGFR del19 and L858R, and BRAF V600E). FISH data revealed presence of MET amplification in 14.2% and of FGFR1 amplification in 20.0%. The association and correlation of these aberrations with clinical findings and prognosis as well as with PD-L1 expression status and mutational load will be presented and outcomes data also give an overview on the presence and clinical characteristics of targetable mutations in advanced SCLC and show, that such mutations occur in a substantial amount of patients. Thus, molecular multiplex diagnostics might be indicated also in SCLC in order to use all therapeutic options available in these patients.

Keywords: squamouscell lung carcinoma, targetable mutations

P2.03B-037 PROGNOSTIC IMPACT OF 1ST-LINE TREATMENT AND MOLECULAR TESTING IN ADVANCED NSCLC IN FRANCE - RESULTS OF THE IFCT-PREDICT.AMM STUDY
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Background: In 2013, recommendations for 1st line treatment in advanced NSCLC included a platinum based chemotherapy (p-CT) with or without bevacizumab (BEV-pCT), an EGFR-TKI, or a non-platinum based CT (non-pCT) depending on clinical, pathological and molecular characteristics. Molecular testing for KRAS, EGFR and ALK is routinely performed in France for advanced non-squamous NSCLC. However, the prognostic impact of the molecular status knowledge before beginning 1st line treatment is unknown. Methods: After a cross-validation study, KRAS, EGFR and ALK molecular status were assessed in 843 consecutive patients (pts) with previously untreated advanced NSCLC. All pts were stage IV. The treatment categories included 4 groups: p-CT, BEVA-pCT, EGFR/ALK TKI and non-pCT. Demographic, clinical and pathological characteristics were collected and pts were followed-up until death. Overall survival (OS) and progression-free survival (PFS) for each line were determined. Prognostic factors including treatment categories (p-CT as reference) and biomarkers status (WT as reference) were studied by Cox model. Results: Treatments were analyzed in 767 (91.0%) of the 843 pts enrolled between 01/2013 and 03/2014. Pts were 93.1% Caucasians, 66.2% males, and median age was 62.4 yr (28-92). 23.6% were never smokers. 21.4% and 90.3% were stage IV. 76.5% had adenocarcinoma, 14.5% squamous cell carcinoma and 9% others with WT=0.4%, KRAS+=23.1%, EGFR/ALK+=10.2%, UD=5.1%, ND=21.2%. 1st line treatments were: p-CT=75.9%, BEVA-pCT=14.2%, EGFR/ALK TKI=7.8% and non-pCT=2.1%. With a 30.3 months (mo) median of follow-up, median OS and PFS were 10.7 mo and 5.3 mo, respectively. Factors independently associated with shorter OS were PS=2 (HR=2.08, p<0.001), KRAS+, UD and ND mutation status (HR=1.40, p=0.02; 1.53, p=0.02; 1.29, p=0.02) and non-pCT as 1st line treatment (HR=1.92, p<0.01), while EGFR/ALK TKI (HR=0.59, p<0.001) was associated with better survival. There was no interaction effect between biomarkers status and OS treatment groups. However, BEVA-pCT in 1st line therapy in KRAS+ and WT NSCLC (p<0.001 and <0.003, respectively) was associated with longer survival compared to p-CT, while giving a TKI or p-CT in WT and KRAS+ NSCLC did not improve OS. Conclusion: Results from the IFCT-PREDICT.amm study suggest that prognosis of advanced NSCLC might be optimized in 1st line setting by the knowledge of EGFR/ALK molecular status and the opportunity to give a BEVA-pCT regimen, especially in patients with KRAS+ and WT tumor.

Keywords: non-small cell lung cancer (NSCLC), KRAS, EGFR, bevacizumab

P2.03B-039 CELL-FREE (CF) DNA AND CFRNA LEVELS IN PLASMA OF LUNG CANCER PATIENTS INDICATE DISEASE STATUS AND PREDICT PROGRESSION

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Background: Cell-free circulating tumor DNA (ctDNA) and RNA (ctRNA) can be extracted from plasma of cancer patients (pts). Measuring dynamic changes in gene expression, allele-fractions of mutations and levels of nucleic acids per ml of plasma in metastatic patients has shown great potential for monitoring disease state and predicting outcome to antitumoral therapy in advanced imaging. Methods: We designed a clinical trial to measure gene levels of plasma ctDNA and ctRNA in metastatic pts with NSCLC, breast, and GI malignancies under treatment and correlate the levels with CT scans done assessing response for one-year clinical trial. ctDNA/ctRNA were extracted from plasma separated from patient whole-blood draw samples at ambient temperature. ctRNA was reverse transcribed with random primers to cdNA. Levels of ctDNA/ctRNA were determined by real-time qPCR. Results of ctDNA/ctRNA tests were compared with responses (CR, PR, SD or PD) as determined by the CT scans. Levels of PD-L1 expression relative to β-actin were determined by qPCR. Results: We have enrolled 39 pts and we are presenting data from 15 pts with NSCLC. The first-line treatments were Carboplatin (60%, 6/15), Opdivo (26.7%, 4/15), Afatinib (13.3%, 2/15), Ceritinib (6.7%, 1/15), Crizotinib (6.7%, 1/15), and Tarceva/Cyramza (6.7%, 1/15). Histological subtypes were 73.3% (11/15) adenocarcinoma, 20% (3/15) squamous, and 6.7% (1/15) other. The majority of patients were Caucasian (66.7%, 10/15), Hispanic (26.7%, 4/15), and African American (6.7%, 1/15). Levels of ctDNA and ctRNA were significantly correlated with one another across patient blood draws (r=0.57, p<0.0001). After the first 2 cycles of therapy, 9 of the 15 patients achieved SD, of whom 8 were analyzed for ctDNA/ctRNA levels. In 7/8 of pts who had SD indicated by CT scan, ctDNA/ctRNA levels were stable, while the 2 PD pts showed significant increases in levels of ctDNA/ctRNA 4.8 weeks prior to progression. In the 2 SD pts treated with Opdivo, PD-L1 expression was stable during the cycles when CT scans also indicated an SD status. Conclusion: In almost 90% of the pts, constant ctDNA/ctRNA levels correlated with stable disease status as seen by CT; moreover, in 2 pts changes in the levels of both ct nucleic acids predicted progression about 5 weeks before CT scans. Importantly, the concordance between ctDNA and ctRNA suggest that ctRNA can just as effective as ctDNA as a prognostic tool, while adding the extra dimension of gene expression.

Keywords: ctDNA, cdNA, plasma, liquid biopsies

P2.03B-040 NANOGRAMS PREDICT POOR OUTCOME IN ADVANCED NON-SMALL CELL LUNG CANCER PATIENTS TREATED WITH PLATINUM-BASED CHEMOTHERAPY

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Background: NANOG is a master transcription factor that regulates embryonic stem cell pluripotency and cell-fate specification though complex interaction with a myriad of factors in signaling pathways. Cumulating evidence suggests that it has oncogenic potential correlating with cell proliferation, clonogenicity, growth, tumorigenicity and invasiveness. Increased NANOG expression has been reported to be related with poor survival in several human malignancies including hepatic, breast, ovarian and colorectal cancers. However, clinical significance of NANOG overexpression in lung cancer has been scarcely evaluated, and correlation between NANOG expression and prognosis in advanced non-small cell lung cancer (NSCLC) has not been studied. The aim of this study is to investigate whether NANOG expression is associated with clinical outcomes of patients who were treated with platinum-based chemotherapy for advanced NSCLC. Methods: To prove NANOG overexpression in lung cancer, we initially assessed the expression of NANOG using Western blotting in lung cancer tissue from NSCLC patients who underwent surgical resection. Then, NANOG expression was examined by immunohistochemistry and evaluated by a semiquantitative histologic score (H score) in tumor tissues from NSCLC patients treated with platinum-based doublet. We performed survival analyses and evaluated the association between NANOG expression and clinical parameters. Results: NANOG expression in lung cancer tissues was significantly increased compared with non-tumorous tissues (p < 0.001). Survival analyses using 110 tumor specimens showed that, at the cutoff value of H score 200, high NANOG expression was significantly associated with short progression-free survival (hazard ratio [HR] = 2.40, 95% confidence interval [CI]: 1.14–5.62), and with short overall survival (HR = 2.89, 95% CI: 2.18–4.62). In similar, result studies were shown in the subgroup analyses for adenocarcinoma and squamous cell carcinoma. NANOG expression was not associated with any clinical parameter including age, gender, smoking status, stage, differentiation, or tumor histology. Conclusion: Increased NANOG expression was associated with poor response and short overall survival in advanced NSCLC patients treated with platinum-based chemotherapy. NANOG overexpression could be a potential adverse predictive marker in this setting.

Keywords: lung cancer, NANOG, transcription factor, Prognosis

P.03B-041 CEREBROSPINAL FLUID TUMOR CELLS FOR DIAGNOSIS OF LEPTOMENINGEAL METASTASES IN NON-SMALL CELL LUNG CANCER
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Background: The diagnosis of leptomeningeal metastases (LM) relied on tumor cells found in cerebrospinal fluid (CSF) and/or typical magnetic resonance imaging (MRI) findings, but both lack sensitivity. The CellSearch Assay™ has been validated to detect CTCs for follow-ups of cancer patients, and we adapted it to identify CSF tumor cells (CSFTCs) in non-small cell lung cancer (NSCLC) with suspected LM, and moreover detected their gene expression and clinical parameters. Results: Twenty-one NSCLC patients with suspicious LM had CSF analyzed through both traditional ThinPrep cytologic test (TCT) and CellSearch, and peripheral blood were detected for circulating tumor cells (CTCs) in fourteen patients. The statuses of EGFR were tested in primary tissues of all twenty-one patients and in CSFTCs of eight patients. Results: All twenty-one patients were identified as LM, CSFTCs were captured by CellSearch in twenty patients (median 969 CSFTCs/7.5 mL, range: 27-14888), while CTCs were captured in only five patients (median 2 CTCs/7.5 mL, range: 2-4), which were much lower than CSFTCs. The sensitivity of CellSearch was 95.2%, while that of TCT from the same CSF puncture was 57.1%, and that of MRI was 52.4%, and that of combined MRI and TCT was 90.5%. Moreover, the specificity of CSFTCs was 100%. Among eight patients with EGFR tested in CSFTCs, six patients matched with primary tissues and resistant gene T790M was identified in two cases.

Conclusion: Cerebrospinal fluid tumor cells could be more sensitive and effective to diagnose LM, and may serve as the potential way of liquid biopsy for EGFR mutation in NSCLC with LM.

Keywords: Cerebrospinal fluid tumor cells, non-small cell lung cancer, Leptomeningeal metastases, EGFR mutations

P.03B-042 MET EXON 14 MUTATIONS ENCODE A HYPERACTIVE KINASE AND THERAPEUTIC TARGET IN LUNG ADENOCARCINOMA
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Background: Activation of the MET tyrosine kinase receptor can drive oncogenesis and metastasis in certain cancer types. Somatic mutations at or around the splice junctions for MET exon 14 (MET14) are a recurrent mechanism of MET activation. MET14 mutations lead to aberrant messenger RNA (mRNA) splicing resulting in a MET14 protein lacking the juxtamembrane domain. Methods: We analyzed RNAseq data across 12 cancer types to define the prevalence of MET14 in solid tumors. We explored the driver role of MET14 both in vitro and in vivo. Finally, we explored acquired resistance mechanisms in a patient treated with crizotinib. Results: The MET14 mutation and aberrant mRNA transcript are most common in lung adenocarcinoma and also identified in other cancers. Endogenous levels of MET14 transcript transform human epithelial lung cells in a HGF-dependent manner. This allele also induces lung cancer in mice that is responsive to a clinically available MET inhibitor. Finally, we document clinical response to crizotinib in a patient with a MET14-driven NSCLC lung cancer. Upon clinical progression on crizotinib, indicating acquired resistance, we detected acquired MET mutations in cell-free DNA from the patient that converge on critical drug-binding residues in the MET activation loop. Conclusion: These findings qualify MET14 mutations as drivers of lung adenocarcinoma, demonstrate the utility of a new animal model of MET-driven disease and identify a subpopulation of patients who may benefit from further development of targeted MET/HGF therapies.

Keywords: MET, Resistance, Targeted therapy, Mouse model
P2.038-043 PERIPHERAL BLOOD CD45RA+ CCR7+ NAÏVE T CELLS WERE CORRELATED WITH PROGNOSIS IN NON- small cell lung cancer patients
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Background: CD45RA+ CCR7+ naïve T cells were reported to generate effectors possessed the high potent cytotoxic activity and low level of “exhaustion” T cells in vitro. However the relationship between frequency of naïve T cells in peripheral blood and prognosis in non-small cell lung cancer (NSCLC) is not clear. In order to elucidate this relationship, we first analyzed the frequency of CD45RA+ CCR7+ naïve T cells in peripheral blood of healthy population and patients with NSCLC. Methods: The frequency of CD45RA+ CCR7+ naïve T cells was calculated by flow cyrometry from healthy volunteers and NSCLC patients. The correlation of naïve T cell frequency and overall survival (OS) of NSCLC patients who were treated with tyrosine kinase inhibitors (TKIs) or chemotherapy was statistically analyzed. Results: 105 healthy volunteers (age range 23-85-year-old) and 137 NSCLC patients (age range 33-86-year-old) were enrolled in our study from 2013 October 1st to 2015 December 1st. Our results showed that the frequency of peripheral blood naïve T cells in NSCLC patients’ Mean±SD (17.6±5.7) was significantly lower than that in healthy subjects’ (Mean±SD 31.2±5.2) (p<0.05). The frequency of naïve T cell was negatively correlated with the frequency of PD-1+CD8+ T cells (R=0.1111, p<0.001) in peripheral blood of NSCLC patients, whereas, which was positively associated with the immune activity of CD8+ T cells and with the frequency of lymphoid stem cells or lymphoid progenitor cells in peripheral blood’s (R=0.1521, p<0.001). In the patients who were treated with TKIs, mOS was significantly lower than that in the healthy subject group’s (Mean±SD 32.8±6.9 vs 31.2±5.2) (p<0.05). Conclusion: In this retrospective cohort of SOM-NSCLC pts, RT combined with LT provided a remarkable median OS of 33 months. These data support radical treatment of the primary tumor including definitive chemoradiation in the setting of SOM-NSCLC.

Keywords: Oligometastatic disease, NSCLC

P2.038-044 TREATMENT OUTCOME AND THE ROLE OF PRIMARY TUMOR THERAPY IN A COHORT OF PATIENTS WITH SYNCHRONOUS Oligometastatic NSCLC
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Background: Although long-term survival was observed in selected patients (pts) with oligometastatic non-small cell lung cancer, the current treatment for those pts remains controversial. This retrospective study aimed to determine the characteristics and the outcome of pts with synchronous oligometastatic NSCLC (SOM-NSCLC) treated in a single center. Methods: SOM was defined as thoracic disease along with ≤3 metastatic lesions. We identified 90 pts in our database that qualified as SOM-NSCLC treated from 2007-2015 at the Catalan Institute of Oncology. Overall Survival (OS) was plotted using Kaplan-Meier method, and multivariate Cox model for prognostic factors was developed. Results: Pts' characteristics are shown in Table 1. Most pts received chemotherapy (31%); 85% platinum doublet and 56% ≥4 cycles. 57 of 50 pts (63%) received thoracic radical therapy (TRT); surgical resection (16%), SBRT (3.5%), concurrent chemoradiotherapy (CRT), and sequential CRT (10.5%). Median OS for all patients was 17.4m (95% CI 9.6 – 25.2). In the multivariate Cox analysis of OS, T extension, histology, smoking history and TRT were independent prognostic factors. As TRT was a highly favourable prognostic factor (HR=0.09, 95% CI 0.20 - 0.80), we looked at the characteristics of pts according to whether they received TRT. Pts treated with TRT had significantly lower number of metastases and metastatic organs involved. 70 of 90 pts (78%) received local therapy (LT) in the metastatic sites: surgery (10%), radiotherapy (6%) or both (29%). Interestingly, pts treated with TRT and LT had significantly longer median OS (12.2 vs. 9.5 months) as compared with other pts (9.3; 95% CI 4.3 - 14.2; p<0.006).

Table 1: Clinical characteristics of pts that received thoracic radical therapies (TRT) and pts not treated with TRT.

Conclusion: In this retrospective cohort of SOM-NSCLC pts, RT combined with LT provided a remarkable median OS of 33 months. These data support radical treatment of the primary tumor including definitive chemoradiation in the setting of SOM-NSCLC.

Keywords: Oligometastatic disease, NSCLC
treatment in SCC lung cancer patients. Such microRNAs could help in decision about the type of palliative chemotherapy - patients with predicted poor treatment effect could be candidates to available clinical trials.  

Keywords: NSCLC, miRNA, chemotherapy, marker

POSTER SESSION 2 - P2.03B: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/IMMUNOTHERAPY
BIOMARKERS – TUESDAY, DECEMBER 6, 2016

P2.03B-046 CLINICOPATHOLOGIC CHARACTERISTICS, GENETIC VARIABILITY AND THERAPEUTIC OPTIONS OF RET REARRANGEMENT PATIENTS IN LUNG ADENOCARCINOMA
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Background: RET fusion gene is identified as a novel oncogene in a subset of non-small cell lung cancer (NSCLC). However, few data are available about the prevalence, clinicopathologic characteristics, genetic variability and therapeutic options in RET-positive lung adenocarcinoma patients. Methods: From 615 patients with lung adenocarcinoma, RET status was detected by reverse transcription-polymerase chain reaction (RT-PCR). Next-generation sequencing (NGS) was performed on positive cases. Thymidylate synthetase (TS) mRNA level was assayed by RT-PCR. Overall survival (OS) was evaluated by Kaplan-Meier method and compared with log-rank test. Results: Twelve RET-positive patients were identified by RT-PCR. However, one patient failed the detection of RET arrangement by FISH and NGS. Totally, the prevalence of RET rearrangement by three methods, including six females and five males with a median age of 54 years. The presence of RET rearrangement was associated with lepidic predominant lung adenocarcinoma subtype in five of 11 patients. RET rearrangements comprised of nine KIF5B–RET and two CCDC6–RET fusions. Four patients had concurrent gene variability by NGS detection, including EGF2R (n=11), MAP2K1 (n=1), CTNNB1 (n=1) and AKT1 (n=1). No survival difference existed between RET-positive and negative patients (58.1 vs. 52.0 months, P=0.504). The median progression-free survival of first-line pemetrexed/platinum regimen was 7.5 months for four recurrent cases, and longer than RET-negative patients (7.5 vs. 5.5 months, P=0.026). The level of TS mRNA was lower in RET-positive patients than that in those RET-negative counterparts (239±18.0% vs. 394±457.0%, P<0.019). Conclusion: The prevalence of RET fusion is approximately 1.8% in Chinese patients with lung adenocarcinoma. RET rearrangement is characterized by lepidic predominance and a lower TS level. RET-rearranged patients may benefit more from pemetrexed-based regimen.

Keywords: Thymidylate synthetase, non-small cell lung cancer, RET, survival

P2.03B-047 THE CLINICAL IMPACT OF MULTIPLE CTDNA GENE ANALYSIS IN LUNG CANCER
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Background: Next-generation sequencing (NGS) of cell-free circulating tumor DNA (ctDNA) enables a non-invasive option for comprehensive genomic analysis of lung cancer patients. Currently there is insufficient data in regard to the impact of ctDNA analysis on clinical decision making. In this study, we evaluate the impact of ctDNA assay on treatment strategy and progression-free survival. Methods: In this retrospective study, data was collected from files of 90 NSCLC patients monitored between the years 2011-2016 at the Thoracic Center Unit at Davidoff Cancer Center, Rabin Medical Center, Israel. The patients performed liquid biopsy NGS analysis by a commercial test (Guardant 360), in which ctDNA was extracted from plasma and analyzed by massively parallel paired end synthesis by digital NGS. This test allows the detection of somatic alterations such as point mutations, indels, fusions and copy number amplifications. Results: Age at diagnosis ranged between 31 and 89 years, with median age of 63 years. Sex ratio was 1.2:2. Out of 90 patients, 38 consecutive patient files have already been reviewed for clinical impact. 82% (31/38) were diagnosed with Adenocarcinoma. 5% (2/38) performed ctDNA at initial diagnosis, 48% (17/38) performed ctDNA after 1st line therapy due to progressive disease and the remaining 50% performed the test after multiple lines of treatment. Liquid biopsy NGS analysis allowed the detection of actionable mutations, according to NCCN guidelines, in 68% (26/38). Treatment decision was changed subsequent to NGS analysis in 34% (13/38) which received tailored targeted therapy. Interestingly, 13% (5/38) were detected with EGFR activating mutation following wild type result by standard local molecular testing based on RT-PCR from tissue biopsy. Based on the RECIST criteria of response evaluation, 30% of the patients had partial response after switching to targeted therapy, 15% had stable disease, 15% experienced progressive disease and ~40% were not evaluated yet. Survival rates will be calculated further in the study based on data availability. Conclusion: Our interim results analysis showed that liquid biopsy ctDNA testing revealed possible treatment options for more than two-thirds of patients analyzed, including FDA-approved drugs as well as eligibility for clinical trials. Most of the patients that were evaluated showed a positive response to targeted therapy. Attention to this topic needs to be further assessed in large randomized controlled trials, these positive results emphasize the utility of liquid biopsy analysis to guide clinicians to select the right therapy for the right patient.

Keywords: non-small cell lung cancer, next generation sequencing, liquid biopsy, personalized medicine

POSTER SESSION 2 - P2.03B: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/IMMUNOTHERAPY
BIOMARKERS – TUESDAY, DECEMBER 6, 2016

P2.03B-048 ACCESS TO BIOMARKER TESTING IN PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER
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Background: Access to biomarker testing is critical for selecting appropriate treatment for patients with advanced non-small cell lung cancer (aNSCLC). This study assessed rates and patterns of biomarker testing among patients with aNSCLC. Methods: Patients aged ≥65 years diagnosed with aNSCLC between 2007-2011 were identified in the SEER-Medicare database and were followed for ≥3 months post-diagnosis (n = 9,651). Patients’ first biopsy within ≤8 weeks of diagnosis was defined as the index date. Biomarker tests included procedure codes for the gene analyses to test for EGFR, ALK, and other mutations. IHC tests, which are mostly used for diagnosis, were excluded. The use of biomarker tests was assessed from the index date until the end of data availability (12/31/2013) or end of Medicare Parts A, B, and D eligibility. Analyzes were replicated in the subgroup with cancer stages IIIb-IV or I and adenocarcinoma, adenosquamous or unknown type of NSCLC histology (n = 6,193). Results: Of 9,651 patients observed for a median of 11 months, 18% had a biomarker test during the follow-up. The use of biomarker testing increased from ≤5% in 2007 to 35% in 2011, and was higher among patients who saw a cancer specialist as compared to those who did not see a cancer specialist. When comparing the patients with and without a biomarker test diagnosed in 2011 (i.e., the most recent year in the data) in the full study sample, a higher proportion of patients without a biomarker test were males (51 vs 43%), non-Hispanic Blacks (13 vs 5%), resided in areas with higher poverty (27 vs 15%) and lower education levels (26 vs 17%), and had larger tumors at diagnosis (median 41 vs 38 mm; p < 0.05 for all). In addition, a lower proportion of them were married (44 vs 52%), resided in big metropolitan areas (51 vs 57%), had stage IV cancer (64 vs 69%), and adenocarcinoma histology at diagnosis (43 vs 77%; p < 0.05 for all). Among tested, >40% of the patients had their first biomarker test ≤8 weeks after biopsy. Results were similar in the subgroup, but the rate of biomarker testing was slightly higher and with slightly shorter delays. Conclusion: Among patients with aNSCLC diagnosed in 2007-2011 a substantial proportion did not undergo biomarker testing or had their biomarker test delayed by ≤8 weeks post-biopsy. Significant differences exist in demographic and cancer characteristics between patients with and without a biomarker test.

Keywords: access to biomarker testing, advanced NSCLC, access to cancer specialty

Abstracts
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**P2.03B-049 MOLECULAR & CLINICAL STATUS OF CURRENT BIOMARKERS: EGFR, ALK, ROS, MET OF LUNG CANCER IN NORTH INDIAN PATIENTS**

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Background: Lung cancer treatment has taken a paradigm shift with advent of molecular therapy. This study evaluates lung adenocarcinoma cases for molecular markers EGFR, ALK, ROS-1 and MET testing. Methods: A total of 4485 cases of lung carcinomas were enrolled from the period of October 2010 to June 2016 in a North Indian tertiary Cancer Centre. Amongst these 815 cases after workup were found to be stage IV adenocarcinoma. Molecular mutation analysis was done for EGFR, ALK, ROS1 and C-MET amplification in 778, 522, 51 and 50 cases respectively. EGFR mutation testing was done using Qiagen Therascreen EGFR kit and Sanger sequencing, ALK testing was done using ALK IHC (clone anti-ALK DSF3), ROS1 gene rearrangement and MET gene amplification using Zytolight DNA FISH probes. The incidence of these biomarkers and its association with the age, sex, smoking history, histological subtype, site of biopsy, treatment history and survival outcome would be analyzed. Results: Late breaking. Will complete information later Conclusion: Late breaking abstract. Will be completed later

**Keywords:** EGFR, ALK, ROS, MET

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**P2.03B-050 PROGNOSTIC VALUE OF HLA-A2 STATUS IN ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC) PATIENTS**

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Background: The class I human leucocyte antigen (HLA) molecules play a critical role as escape mechanism of antitumoral immunity. Indeed, novel immune-targeting cancer vaccines are currently developed in HLA-A2 positive patients for modulating the T cells response. The HLA-A2 status has been proposed as prognostic factor in lung cancer, but previous evidence is inconsistent. The aim of this study is to evaluate the role of HLA-A2 status as prognostic factor in a large cohort of advanced NSCLC patients. Methods: Advanced NSCLC patients eligible to platinum based chemotherapy (CT) were included from Oct. 2009 to July 2015 in the prospective MSN study (IDRCB A2008-A00373-52) in our institute. HLA-A2 status was analyzed. Results: Late breaking. Will complete information later. Conclusion: Our study has observed no prognostic role of HLA-A2 status in advanced NSCLC patients.

**Keywords:** EGFR, ALK, ROS, MET

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**P2.03B-051 TXR1: A NOVEL BIOMARKER PROVED TO BE PROGNOSTIC FACTOR AND EVIDENCE TO PROVIDE NEWLY TREATMENT STRATEGIES IN METASTATIC EGFR WILD-TYPE NSCLC**

Yongchang Zhang

Human Cancer Hospital, Changsha/China

Background:

Deregulating cellular energetics is one promising hallmark of cancer and Thoredoxin reductases 1 (TrxR1) plays a key role in cell metabolism [1-4]. It was found in our previous study that the activity of TrxR1 in serum is significantly higher in cancer patients than volunteers (table), based on 1122 cancer patients VS 84 volunteers. However, the role of TrxR1 in prognosis and evaluation of treatment in EGFR wildtype non-small cell lung cancer need to be investigated. Methods: In cohort one, serum level of TrxR1 in 127 metastatic EGFR wide type NSCLC patients was measured by ELISA assay before receiving first line standard doublet chemotherapy with PP and GP included. In cohort two, a phase IC clinical trial was conducted to compare the TrxR1 inhibitor (BBSKE) and placebo in advanced NSCLC patients with EGFR wildtype mutation and high activity level of TrxR1 after first line and second line treatment. Patients in cohorts one and two were from NCT01980212, NCT01991418 and NCT02166242. Survival data were collected in cohort one and two. Results: Survival data analysis in cohort one showed that the PFS of lower TrxR1 activity group was significantly long compared to the higher in the total (mPFS 5.0m vs 3.1m, p=0.029), and also in adenotype and squamous subtype. The same tendency was observed in OS (mOS 15.0m vs 12.5m), but the date were not mature yet. Results in cohorts two show that patients with high level activity of TrxR1 can benefit more from BBSKE (data were not mature). Conclusion: Human with high level TrxR1 may have the high risk to suffer from NSCLC. High level of TrxR1 may suggest poor prognosis in metastatic EGFR wild-type non-small-cell lung cancer patients. Further clinical studies are warranted to profile TrxR1 inhibitors from bench to bedside.

**Keywords:** TrxR1, metastatic EGFR wild-type NSCLC, BBSKE, biomarker

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**P2.03B-052 XRCCL1 ARG399GLN AND RAD51 GENE POLYMORPHISMS IN ADVANCED LUNG ADENOCARCINOMA IN SERBIA**

Jelena Spasic1, Nemanja Stanic2, Davorin Rasdovojic1, Ana Kriковуca2, Mira Kuburovic2, Bojan Zaric3, Bransilav Perin1, Sinisa Radulovic2, Radmila Jankovic2, Milena Cavic2

1Clinic for Medical Oncology, Institute for Oncology and Radiology of Serbia, 2Institute for Oncology and Radiology of Serbia, Belgrade/Serbia, 3Clinic for Thoracic Oncology, Institute for Pulmonary Diseases of Vojvodina, Faculty of Medicine, University of Novi Sad, Sremska Kamenica/Serbia

Background: XRCCL1 and Rad51 are proteins involved in DNA base excision repair and DNA homologous recombination/double-stranded-break repair mechanisms respectively. In non-small cell lung cancer, XRCCL1 Arg399Gln polymorphism (disrupts protein-protein interactions), and Rad51 G535C polymorphism (enhances Rad51 promoter activity), have been proposed as factors that influence the overall and progression-free survival (OS and PFS)
of patients treated with platinum-based chemotherapy. This study aimed to evaluate the influence of XRCC1 Arg399Gln and Rad51 G135C polymorphisms on the toxicity of chemotherapy and clinical outcome (OS, PFS) of advanced lung adenocarcinoma patients in Serbia. Methods: The study included 150 cases of advanced lung adenocarcinoma patients, EGFR wild type, stage IIIb/IVTNM7, performance status 0, 1 or 2, of Caucasian descent, who underwent standard platinum-based chemotherapy. XRCC1 and Rad51 genotyping was done by PCR-RFLP. Statistical analysis was performed using Chi-square, Fisher’s exact, Wilcoxon rank sum test, Breslow-Day test. Survival methodology was used for OS and PFS (Kaplan-Meier product limit method and Log-Rank test, Cox regression for HR). Statistical significance was considered for p<0.05. Results: The group consisted of 62 males (66%) and 32 females (34%), median age at diagnosis 61 years (range 37-84), with 77% (82 of) current or ex-smokers, and 55% of which presented with metastases at diagnosis. Follow up period was 155 months (median 11 months), during which 76 patients (81%) progressed, and 24 (19%) experienced chemotherapy-related toxicity of grade 3 and 4. Median (95% CI) PFS was 8.1 months (7.1-9.1), and median OS was 10 months (8.2-11.7). Genotype frequencies for XRCC1 Arg399Gln were 39.4% for Arg/Arg, 25.5% for Arg/Gln and 35.1% for Gln/Gln genotype. For Rad51 G135C frequencies were 61.7% for G/G, 26.6% for G/C and 11.7% for C/C genotype. Carriers of the XRCC1 Gln allele had a significantly shorter PFS (7.2m vs 9.5m, Breslow p=0.023) and OS (6.4m vs 15.7m, Breslow p=0.04), and were more susceptible to progression during chemotherapy. Although Rad51 genotypes alone had no statistically significant effect on PFS and OS, carriers of both XRCC1 Gln allele and Rad51 C allele had a 4 months shorter OS, the difference was not statistically significant. There were no statistically significant differences in the occurrence of high grade chemotherapy-induced toxicity according to XRCC1 and Rad51 genotypes. Conclusion: These results suggest that in the Serbian population XRCC1 and Rad51 genotyping could be a useful tool for predicting the clinical outcome with platinum-based chemotherapy in advanced EGFR wild-type adenocarcinoma patients.

Keywords: Rad51, polymorphisms, treatment-related toxicity, XRCC1
Abstracts

But whether its prognostic value was influenced by other factors was never discussed before. The aim of this study was to evaluate the influence of albumin level on the prognostic value of the baseline NLR. Methods: A total of 325 patients were retrospectively enrolled from October 2007 to October 2014. The baseline and demographic factors were recorded. The NLR was calculated using the white blood cell count ratio. The cutoff of NLR was determined by the receiver operator characteristics analysis. The patients were dichotomized into high (≥ 3.19) and low (< 3.19) NLR groups. Both groups had similar demographic features. However, the low group had longer OS (22.3 m) than the higher one (13.1 m; P < 0.001). Interestingly, it was also found that the albumin level had an impact on its prognostic value. For patient with compromised albumin level (≤ 35 g/L), NLR had no relationship with the OS (P = 0.380). However in patients with normal albumin level (> or ≥ 35 g/L), high NLR strongly indicated poor OS (13.6 m vs 24.5 m; P < 0.001). Conclusion: This study argued the NLR was a convenient prognostic marker, but its prognostic value was influenced by albumin level.

Keywords: Prognosis, NLR, NSCLC, albumin

P2.03B-055 SURVIVAL IN NON-SMALL CELL LUNG CANCER (NSCLC) PATIENTS (PTS) WITH DRIVER MUTATIONS AT SANDTON ONCOLOGY CENTRE, SOUTH AFRICA

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Background: The administration of tyrosine kinase inhibitors (TKI) has changed the treatment of NSCLC pts with driver mutations. In the Lung Cancer Mutation Consortium study, survival was significantly better for those with an oncogenic driver which received a TKI compared to those who did not. Methods: Retrospective records review was performed on NSCLC pts treated at Sandton Oncology Centre (SOC), between 1/1/2010 and 31/12/2015. Results: There were 176 lung cancer pts in total, of which 25 were small cell and 151 NSCLC. 129 pts (85%) had non-squamous pattern (hematoxylin-eosin stain) and CD8 and FOXP3 positive cell counts ratio. It has also been shown that inflammatory/immune cells (IC) in tumor microenvironment have an important role in tumor development and outcome. Several biomarkers reflect this inflammatory response, notably, Tumor Infiltrating Lymphocytes (TILs), Neutrophil-Lympocyte ratio (NLR), and platelet to lymphocyte ratio (PLR). The current study aimed to evaluate the influence of the NLR, MLR, PLR, and IC infiltration as prognostic factors in mNSCLC. Methods: We retrospectively collected clinical, pathological and demographical data from the medical charts of mNSCLC patients, diagnosed between Jan 1st 2011 and July 30th 2014, from a single Brazilian institution. When patients were dichotomized into high (> or ≥ 3.19) and low (< 3.19) NLR groups. Both groups had similar demographic features. However, the low group had longer OS (22.3 m) than the higher one (13.1 m; P < 0.001). Interestingly, it was also found that the albumin level had an impact on its prognostic value. For patient with compromised albumin level (≤ 35 g/L), NLR had no relationship with the OS (P = 0.380). However in patients with normal albumin level (> or ≥ 35 g/L), high NLR strongly indicated poor OS (13.6 m vs 24.5 m; P < 0.001). Conclusion: This study argued the NLR was a convenient prognostic marker, but its prognostic value was influenced by albumin level.

Keywords: Biomarkers, NSCLC

P2.03B-057 DIAGNOSTIC VALUE OF TUMOR MARKERS IN LUNG ADENOCARCINOMA-ASSOCIATED CYTOL OLOGICALLY POSITIVE AND NEGATIVE PLEURAL EFFUSIONS

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Background: Cytology fails to detect neoplastic cells in 40–50% of malignant effusions (PEs), which commonly accompany lung adenocarcinomas. Methods: PE samples were collected from 74 lung adenocarcinoma patients with associated cytologically positive (41) and negative (33) effusions, and from 99 patients with benign conditions including tuberculosis, pneumonia, congestive heart failure, and liver cirrhosis. We evaluated the diagnostic sensitivity and optimal cutoff points for tumor markers Her-2/neu, Cyfra 21-1, and carcinoembryonic antigen (CEA) to distinguish lung adenocarcinoma-associated cytologically negative pleural effusions (LAC-CNPEs) from benign PEs. Results: Mean levels of Her-2/neu, Cyfra 21-1, and CEA were significantly higher in LAC-CNPEs than in benign pleural effusions (P = 0.0050, = 0.0039, and = 0.0001, respectively). The cutoff points for Her-2/neu, Cyfra 21-1, and CEA were optimally set at 3.6 ng/mL, 60 ng/mL, and 6.0 ng/mL. Their sensitivities ranged from 12.1% to 30.3%, to 63.6%, respectively. CEA combined with Cyfra 21-1 increased diagnostic sensitivity to 66.7%. Conclusion: Combining CEA with Cyfra 21-1 will provide the best differentiation between LAC-CNPEs and benign PEs with two tumor markers to date, and allows early diagnosis and early treatment for two-thirds of affected patients.

Keywords: CEA, Cyfra 21-1, carcinoembryonic antigen, HER-2/neu, paraneoplastic

P2.03B-058 BLOOD CELL COUNT RATIOS AT DIAGNOSIS AS PROGNOSTIC MARKERS IN PATIENTS WITH METASTATIC NON-SMALL CELL LUNG CANCER (MNSCLC)

Eliza Ricardo1, Bianca Boneti1, Taynan Ribeiro1, Rafael De Moraes1, Helano Freitas2, Alexandre Da Costa3, Victor Andrade1, Vladimir Cordeiro De Lima1

Background: Systemic inflammation has been linked with cancer development and outcome. Several biomarkers reflect this inflammatory response, notably, the Neutrophil-Lymphocyte ratio (NLR), Monocyte-Lymphocyte ratio (MLR), and platelet to lymphocyte ratio (PLR). The current study aimed to evaluate the influence of the NLR, MLR, PLR, and IC infiltration as prognostic factors in mNSCLC. Methods: We retrospectively collected clinical, pathological and demographical data from the medical charts of mNSCLC patients, diagnosed between Jan 1st 2011 and July 30th 2014, from a single Brazilian institution. When patients were dichotomized into high (> or ≥ 3.19) and low (< 3.19) NLR groups. Both groups had similar demographic features. However, the low group had longer OS (22.3 m) than the higher one (13.1 m; P < 0.001). Interestingly, it was also found that the albumin level had an impact on its prognostic value. For patient with compromised albumin level (≤ 35 g/L), NLR had no relationship with the OS (P = 0.380). However in patients with normal albumin level (> or ≥ 35 g/L), high NLR strongly indicated poor OS (13.6 m vs 24.5 m; P < 0.001). Conclusion: This study argued the NLR was a convenient prognostic marker, but its prognostic value was influenced by albumin level.

Keywords: Biomarkers, NSCLC
by immunohistochemistry (IHC). NLR, MLR and PLR were defined as the ratio between the absolute neutrophil, monocyte or platelet to lymphocyte blood counts. Overall survival (OS) was calculated from the time of CT start for metastatic disease till death by any cause. Association between clinical variables and NLR/MLR/PLR was tested with Chi-square or Fisher’s exact test. OS curves were generated by Kaplan–Meier method and compared using log-rank test. Multivariate analysis was performed using Cox regression (backward stepwise method) to assess variables independently associated with OS. P values < 0.05 were considered statistically significant. Results: A total of 170 patients were included in the study. Median age was 63.4 years, 54.1% were male, 80.6% had adenocarcinoma, 17.1% had modified EGFR, 73.3% were current/former smokers, and 78.2% had ECOG ≥1. Median values for NLR, MLR and PLR were 4.6, 0.419 and 215, respectively. 114 (67.1%) patients had samples available for IC analysis and 88 for HC, 39% had moderate to strong IC (IC2/3) infiltrate and 91.2% had a monoclonal predominant infiltration pattern. Median follow-up time was 19.64 months (mo) and median overall survival was 13.6 mo. NLR > 4.6 (95% CI: 19.05 mo, p < 0.001) and PLR > 215 (8.69 vs. 8.70, p = 0.014) were associated with poor OS. IC2/3 was associated with shorter OS (IC1 13.63mo vs. 4.6mo IC2/3, p = 0.006), while mononuclear IC pattern was associated with improved survival (13.6 vs. 4.6 mo, p < 0.023). CD8 and FOXP3 positive cells were not associated with OS. In multivariate analysis, the NLR remained as an independent prognostic factor for worse OS (HR 2.71 IC95% 1.39-5.25, p = 0.003). Conclusion: Elevated NLR is an independent predictor of poor OS in patients with advanced NSCLC.

Keywords: inflammatory infiltration, metastatic non-small cell lung cancer, Blood cell count ratios, prognostic markers

P2.03B-059 DETECTION OF CIRCULATING TUMOR CELLS USING MULTIPLE mRNA IN SITU HYBRIDIZATION PREDICTS METASTASIS IN NON-SMALL CELL LUNG CANCER
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Background: Peripheral blood circulating tumor cells (CTCs) are involved in tumor distant metastasis. According to different cell surface markers, CTCs can be divided into epithelial phenotype (EP), hybrid epithelial/mesenchymal phenotype (EMP) and mesenchymal phenotype (MP). An epithelial to mesenchymal transition (EMT) is a process which epithelial cells lose their polarized organization and acquire migratory and invasive capabilities. Emerging evidences have indicated that CTCs with mesenchymal phenotype play important role on cancer metastasis. This study aimed to evaluate the ability of CTCs to detect distant metastases in non-small cell lung cancer (NSCLC). Methods: This study was performed between September 2014 and December 2015. Patients were considered for enrollment and were enrolled in this study if they met the following criteria: 1) histologically confirmed NSCLC; 2) patients who did not undergo any treatment; 3) patients at 18 to 85 years old. Blood samples were collected within 14 days before or after radiotherapy. CTCs detection was performed by multiple mRNA in situ hybridization. The ability of CTCs in detection of distant metastasis was compared with radiographic results. The counts of different CTCs phenotype were applied by Logistic regression equation, distant metastasis was determined with P < 0.5, when 0 < P < 0.5 was diagnosed of no distant metastasis. Results: In total, fifty-nine patients were enrolled. 15 were females and 44 were males. There are 6, 11, and 22 patients diagnosed as stage I, II, III, and stage IV, respectively. Adenocarcinoma accounts for 49.2% (29 cases), 22% (13 cases) for squamous, and 5.3% (3 cases) for adenosquamous. The median of total CTCs detected was 5 counts (0 to 57), 2 counts (0 to 14) for EP, 2 counts (0 to 45) for EMP, and 0 count (0 to 10) for MP. The counts of different CTCs phenotype showed no significant difference in gender, age and pathological type. In patients with stage IV, the detection rate of MP was much higher. Compared with radiographic examination, CTCs detection showed a sensitivity of 75.00%, and the specificity of 71.43%. The overall concordance was 72.24%, indicating reliability of CTCs detection of tumor distant metastasis. Conclusion: CTCs detected by multiple mRNA in situ hybridization has well ability in detection of tumor distant metastasis. It might have clinical potential in the future application.

Keywords: mRNA ISH, CTC, NSCLC, distant metastasis

P2.038-060 BASELINE SKELETAL MUSCLE INDEX (SMI) VALUES ARE ASSOCIATED WITH BIOMARKERS OF INSULIN RESISTANCE IN STAGE IV NON-SMALL CELL LUNG CANCER
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1Hematology, Oncology and Cell Therapy, Rush University Medical Center, Chicago/IL/United States of America, 2Rush University Medical Center, Chicago/IL/United States of America, 3Rush University Medical Center, Chicago/IL/United States of America, 4Rush University Medical Center, Chicago/IL/United States of America, 5Hematology/Oncology, Rush University Medical Center, Chicago/IL/United States of America, 6Hematology, Oncology and Cell Therapy, Rush University Medical Center, Chicago/IL/United States of America

Background: The aim of this project was to correlate pretreatment levels of circulating biomarkers of insulin resistance with computed tomography measured evidence of sarcopenia in stage IV NSCLC patients receiving platinum doublet chemotherapy. Methods: Pretreatment serum from 93 patients with frontline stage IV NSCLC was evaluated for 13 metabolism biomarkers with the Bio-Plex Pro Human Diabetes Assay Panel and 20 inflammation-related biomarkers using the Milliplex Human High Sensitivity C-Cell Panel. All patients were treated with platinum chemotherapy. All patients had skeletal muscle index (SMI) calculated from baseline CT images using the Slice-O-Matic software package (Tomovision); where SMI = (muscle cross sectional area in cm2) / height in m2. Associations of biomarkers with SMI were assessed using a Spearman’s Rank Correlation Coefficient. The Log-rank test was performed to evaluate the association of different biomarkers with overall survival (OS). Results: High levels of adiponectin (with low levels of adiponectin being correlating with obesity in the literature) were associated with good OS (p = 0.036) and low baseline SMI value specifically for males (p = 0.0029). High levels adiponectin was associated with favorable OS (p = 0.015) and a higher baseline SMI specifically for females (p = 0.56 x 10-5). Low levels of ghrelin were associated with favorable OS (p = 0.005) and were inversely associated with SMI values for both genders (p = 0.021). Conclusion: Altered values of several biomarkers of insulin resistance were associated with inferior survival and a greater degree of sarcopenia in frontline NSCLC patients receiving platinum double therapy. These findings suggest a certain subset of patients that may have improvements in cancer cachexia by targeting insulin resistance.

Keywords: non-small cell lung cancer, skeletal muscle index, sarcopenia, insulin resistance markers

P2.03B-061 BASELINE NEUTROPHIL–LYMPHOCYTE RATIO IS RELATED TO BASELINE PRESENCE OF BRAIN METASTASES AND SUBSEQUENT BRAIN METASTASES IN STAGE IV NSCLC
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1Department of Pathology, Ajou University School of Medicine, Suwon/Korea, Republic of, 2Department of Hematology-Oncology, Ajou University School of Medicine, Suwon/Korea, Republic of

Background: We examine the predictive value of neutrophil–lymphocyte ratio (NLR) by examining their association with baseline presence and subsequent development of brain metastases in patients with stage IV non-small-cell lung cancer (NSCLC). Methods: We examined the predictive value of NLR for brain metastases in 263 stage IV NSCLC using the receiver operating characteristic (ROC) curve analysis for optimal cut-off value. Logistic regression models were used to determine the association of NLR with the baseline presence of brain metastases. For patients without brain metastases at diagnosis, a competing risk analysis was performed, calculating the probability of brain metastasis in the presence of the competing risk of mortality by other causes using Gray’s test. Results: The median follow-up time was 11 months (range: 1–95 months). Univariate analysis reveals that patients with high NLR (≥4.95) had significantly more brain metastases at diagnosis than those with low NLR (P = 0.038), multivariate analysis was not performed because there was no significant risk factor for predicting brain metastases at diagnosis, except NLR. In patients who did not have baseline brain metastasis, competing risks analysis reveals that patients with high NLR showed higher cumulative incidence of subsequent brain metastases, compared to those with patients with low NLR (P = 0.02). A high NLR was associated with the baseline presence or the subsequent development of brain metastases, particularly in the group with adenocarcinoma (P = 0.016 and P = 0.04, respectively). Furthermore, an increase in NLR during treatment was associated with
Background: Survival of lung cancer (LC) patients has increased and it is important to assess disease and treatment related symptoms that could negatively impact on prognosis and health-related quality of life (HRQL). The FAACT questionnaires have been proposed as a useful tool to measure HRQL, it includes 5 subscales: physical (PWB), emotional (EWB), functional (FWB) and social well-being (SWB), and AC/S-12 which is used to diagnose anorexia cachexia syndrome (CACS). The aim of this study was to associate the FAACT total score and subscales with clinical outcomes and survival. Methods: A cohort of patients with LC completed the FAACT instrument; regardless of age, gender, line of treatment, number of cycle, performance status, or histopathology subtype. Clinical and biochemical variables were collected. Survival was estimated from the day of questionnaire application until death or last follow-up. Results: The study included 200 patients. FAACT subscales had association with several clinical and biochemical data that are show in Table 1. PWB, FWB, AC/S-12 and FAACT total score were strongly associated to overall survival.

Conclusion: The FAACT questionnaire is reliable and valid for the assessment of HRQL and CACS in patients with LC and can be used liberally in clinical trials.

Keywords: health related quality of life, anorexia cachexia syndrome

Table 1. Association of FAACT and subscales with clinical outcomes (p < 0.05).

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Figure 1. Kaplan-Meier survival curve of patients depending on the scores of FAACT subscales and total scale (a=200).

Figure 2. Kaplan-Meier survival curve of patients depending on the scores of FAACT subscales and total scale (b=300).

Figure 3. Kaplan-Meier survival curve of patients depending on the scores of FAACT subscales and total scale (c=400).

Figure 4. Kaplan-Meier survival curve of patients depending on the scores of FAACT subscales and total scale (d=500).
to November 2015, have been included in the study. Baseline information were collected about molecular profiling performed and therapies. Results: A total of 1787 patients were enrolled (64% males, 36% females; median age 67 years; 22% never smokers, 31% current smokers, 42% former smokers, 75% adenocarcinoma, and 73% with PS ECOG 0 or 1). The 7.3% of diagnosis was histological, while 26.1% was cytological. 1382 (77%) patients were tested for one or more molecular analysis during the history of disease, for a total of 3532 molecular tests. Only 405 patients did not receive any molecular test. 32.3% of patients presented a genetic alteration: EGFR mutation was reported in 17.8% of cases (319/1787), ALK translocation in 8.8% (82/926), KRAS mutation in 31.9% (514/1628), MET amplifications in 15.8% (10/63), BRAF mutations in 3.7% (9/241), ROS1 translocation in 4% (11/269), HER2 mutation in 3.3% (3/89) of cases and FGFR alteration was found in 3 cases (only 15 tested). Considering patients younger than 45 years, never smokers and females, an EGFR alteration was detected in 25.4%, 43.5% and 30.6%, respectively. While 15.6%, 9.5% and 6.3% were ALK rearranged, respectively. For patients receiving an EGFR tyrosine-kinase inhibitor as first-line treatment, among those whose data are evaluable (79.2%), the median interval from diagnosis to first-line was 35 days. EGFR mutated patients received first-line erlotinib, gefitinib and afatinib in 9.4%, 39.1% and 33.8% of cases, respectively. At time of analysis, ALK rearranged patients received an ALK inhibitor (crizotinib, alectinib or ceritinib) as first- and second-line in 71.9% of cases. 26.3% of all patients received a maintenance therapy, mainly with pemetrexed (37.2% of cases). Conclusion: Routine molecular assessing is properly performed according to the national guidelines. A selection bias in including only those patients performing molecular tests, may explain the high proportion of patients with a molecular alteration. The low number of patients tested for ALK could be partially related to the impossibility to prescribe Crizotinib in first-line. In more than 70% of cases EGFR mutated patients received gefitinib or afatinib as first-line treatment.

Keywords: molecular test, Italian cohort, lung

**POSTER SESSION 2 – P.03B: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/IMMUNOTHERAPY BIOMARKERS – TUESDAY, DECEMBER 6, 2016**

**P2.03B-064 GENOMIC PROFILING IN NON SMALL CELL LUNG CANCER: NEW HORIZON FOR PERSONALIZED MEDICINE**

Satheesh Thungappa1, Shekar Patil1, H Shashidhara1, Mithua Ghosh2, SHEela L1, Siddesh Southekal2, Upasana Mukherjee1, Vidya Veldore2

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Background: Lung cancer is a rich in molecular complexities and spurred by different molecular pathways. Personalized medicine has begun to bring new hope to people with lung cancer, especially non-small cell lung cancer (NSCLC). Personalized medicine involves looking at the cells obtained from a biopsy to see if there are any genetic mutations able to exploit these unique pathways to develop targeted therapies. Very few publications are there from molecular test.

Types of mutations | Number of cases
---|---
TP S3 | 18
EGFR | 7
EGFR, 7990M | 3
PIK3CA | 4
K-RAS | 4
N-RAS | 1
KDR | 2
RET | 2
PTEN | 3
MPL | 1

Out of 35 positive patients, 13 had two mutations and 43.75% could offer targeted therapy. 38% of them responded to therapies who were treated with targeted drugs. Conclusion: There is a potential role for PIK3CA, EGFR +/− 7990M, KDR, RET and PTEN as therapeutic targets as personalized therapy in NSCLC. Present study helps us in understanding the diversity of molecular drivers in lung cancer and its clinical management for these patients, along with understanding of prognosis.

Keywords: NSCLC, NGS, mutations

**P2.03B-065 SERUM AND BRONCHOALVEOLAR LAVAGE LEVELS OF ADIPOGENIC IN ADVANCED NON-SMALL CELL LUNG CANCER: RESULTS OF A PROSPECTIVE STUDY**

Paraskevi Boura, Dimitra Grapsa, Stylianos Loukides, Apostolos Achimastos, Kostas Syriros

Background: Adiponectin (APN) is a major adipokine synthesized by the adipose tissue. A significant body of preclinical evidence has documented the involvement of APN in molecular pathways with a key role in carcinogenesis, while some, but not all, previous clinical studies have suggested the potential value of this molecule as a biomarker of diagnosis and/or prognosis in various malignancies, mainly including obesity-related solid tumors. The main objective of this study was to further explore the prognostic implications of APN levels in the serum and bronchoalveolar lavage of patients with advanced non-small cell lung cancer (NSCLC). Methods: Twenty-nine (29) consecutive newly diagnosed NSCLC patients with stage IV disease were prospectively enrolled. Serum and BAL levels of APN were obtained at baseline (before initiation of any therapeutic intervention) and assayed by enzyme-linked immunosassay (ELISA). Serum and BAL levels of APN were correlated with standard clinicopathologic parameters, including gender, age, body mass index (BMI), weight loss, size, histology and grade of the primary tumor, pathologic nodal status and performance status (PS). The association of each study variable with overall survival (OS) was assessed by univariate and multivariate Cox regression analyses. Results: Mean age of patients was 65.6 years (SD=10.1 years), while the majority were male (24/29 cases, 82.8%). The predominant histological type was adenocarcinoma (18/29 cases, 62.1%). PS was 0 and ≥1 in 17/29 (58.6%) and 12/29 (41.4%) patients, respectively. Weight loss more than 10% was noted in 10/29 patients (34.5%). Median serum and BAL APN levels were 911.5 ng/ml and 17710 ng/ml, respectively. No significant correlation were observed between the serum or BAL levels of APN and the clinicopathologic parameters evaluated. Univariate Cox regression analysis showed that APN levels were not significantly associated with survival. The only prognostic factor identified, both by univariate and multivariate survival analysis, was PS. Conclusion: The results of our prospective cohort failed to reveal any significant associations between serum or BAL levels of APN and several prognostic parameters (including OS) in stage IV NSCLC, thus confirming most previous observations.

Keywords: serum, bronchoalveolar lavage, non-small cell lung cancer, adiponectin

**P2.03B-066 DIAGNOSTIC VALUE OF PLEURAL CYTOLOGY TOGETHER WITH PLEURAL CEA AND VEGF IN PATIENTS WITH NSCLC AND LUNG METASTASES FROM BREAST CANCER**

Franco Lumachi1, Paolo Ubiali2, Renato Tozzi2, Sandro Sulfaro1, Stefano Basso2

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Out of 35 positive patients, 12 had two mutations and 43.75% could offer targeted therapy. 38% of them responded to therapies who were treated with targeted drugs. Conclusion: There is a potential role for PIK3CA, EGFR +/− 7990M, KDR, RET and PTEN as therapeutic targets as personalized therapy in NSCLC. Present study helps us in understanding the diversity of molecular drivers in lung cancer and its clinical management for these patients, along with understanding of prognosis.

Keywords: NSCLC, NGS, mutations

**POSTER SESSION 3 – P.03B: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/IMMUNOTHERAPY BIOMARKERS – TUESDAY, DECEMBER 6, 2016**

**P2.03B-067 DIAGNOSTIC VALUE OF PLEURAL CYTOLOGY TOGETHER WITH PLEURAL CEA AND VEGF IN PATIENTS WITH NSCLC AND LUNG METASTASES FROM BREAST CANCER**

Franco Lumachi1, Paolo Ubiali2, Renato Tozzi2, Sandro Sulfaro1, Stefano Basso2

1Department of Surgery, Oncology & Gastroenterology, University of Padua, School of Medicine, Padova/Italy, 2Department of Surgery, General Surgery, S. Maria Dei Angeli Hospital, Pordenone/Italy, 3Department of Laboratory Medicine, Clinical Pathology Laboratory, S. Maria Dei Angeli Hospital, Pordenone/Italy, 4Department of Laboratory Medicine, Pathology and Histopathology, S. Maria Dei Angeli Hospital, Pordenone/Italy

Out of 35 positive patients, 12 had two mutations and 43.75% could offer targeted therapy. 38% of them responded to therapies who were treated with targeted drugs. Conclusion: There is a potential role for PIK3CA, EGFR +/− 7990M, KDR, RET and PTEN as therapeutic targets as personalized therapy in NSCLC. Present study helps us in understanding the diversity of molecular drivers in lung cancer and its clinical management for these patients, along with understanding of prognosis.

Keywords: NSCLC, NGS, mutations
Background: Pleural effusion (PE) is common in patients with advanced non-small cell lung cancer (NSCLC) and lung metastases from breast cancer, accounting for at least 20-30% of cases. Unfortunately, many patients with malignant PE exhibit a negative pleural cytology (PC), and thus further invasive diagnostic procedures, including VAT-guided biopsy, are required. The aim of this study was to evaluate the diagnostic value of PC together with pleural carcinoembryonic antigen (pCEA) and vascular endothelial growth factor (pVEGF) assay in cancer patients with PE. Methods: Thirty-six patients with suspicious PE scheduled to undergo VAT-guided biopsy underwent both PC and pCEA and pVEGF measurement before surgery. There were 20 (55.6%) males and 16 (44.4%) females, with an overall median age of 67 (range 40-82 years). Patients with non-diagnostic cytology were excluded from the study. pCEA was measured with automated method of immuno-chemiluminescence (LDC, Dimension Vista, Siemens HD, Camberley, UK), while pVEGF with an enzyme-linked immunosorbent assay (ELISA) commercially available kit. 

According to previously obtained data from laboratory archival information, the optimum cutoff levels were 5 ng/mL and 6 ng/mL for pCEA and pVEGF, respectively. Results: Final pathology showed 10 (27.8%) patients with NSCLC, 13 (36.1%) with lung metastases, and 13 (36.1%) with benign PE. The age did not differ between groups (p=0.59). The sensitivity, specificity and accuracy of PC, and pleural CEA and VEGF are reported in the Table. The area under the curve (AUC) of the ROC curve of PC+pCEA+pVEGF in combination was 0.921 (95% CI: 0.913-0.973), and the diagnostic accuracy was 97.2%.

RESULTS

<table>
<thead>
<tr>
<th>Cytology, pCEA, pVEGF</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Negative Predictive Value</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytology+pCEA+pVEGF</td>
<td>65.2% (45.7-84.7)</td>
<td>92.3% (77.7-99.9)</td>
<td>93.7% (81.5-99.9)</td>
<td>75.0%</td>
</tr>
<tr>
<td>pCEA</td>
<td>73.9% (56.0-91.9)</td>
<td>92.3% (77.7-99.9)</td>
<td>66.7% (44.9-88.4)</td>
<td>80.5%</td>
</tr>
<tr>
<td>pVEGF</td>
<td>78.3% (61.4-95.1)</td>
<td>92.3% (77.8-99.9)</td>
<td>70.6% (68.9-92.2)</td>
<td>83.3%</td>
</tr>
<tr>
<td>PC+pCEA+pVEGF</td>
<td>95.6% (87.3-99.9)</td>
<td>100%</td>
<td>92.9% (79.4-99.9)</td>
<td>97.2%</td>
</tr>
</tbody>
</table>

Conclusion: In patients with PE, according to our results, the measurement of pleural CEA and VEGF, and PC evaluation together reached a very good accuracy and 100% specificity, and should be suggested in all cancer patients when a noninvasive evaluation of a PE is required as non-invasive procedure.

Keywords: NSCLC, CEA, VEGF, Pleural cytology

POSTER SESSION 2 – P2.038 ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/IMMUNOTHERAPY BIOMARKERS – TUESDAY, DECEMBER 6, 2016

P2.038-067 PREDICTORS OF ADVANCED SQUAMOUS CELL LUNG CANCER PRIOR TO BIOPSY: BIOLOGICAL BEHAVIOR AND PROGNOSTIC FACTORS

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Background: Squamous cell lung cancer (SqCLC) has a unique clinical-pathologic criteria in comparison to other non-small cell lung cancer (NSCLC). SqCLC is infrequently reported in depth as a separate category in the literature. This study aims to identify patients with SqCLC prior to biopsy and understand clinicopathologic criteria of SqCLC vs others. Methods: Among enrolled SqCLC cases attending National Cancer Institute (NCI)– Cairo University (2012–2014), we retrospectively reviewed those who had SqCLC. Data regarding demographics, ECOG-performance status (PS), tumor histology, grade and stage, chemotherapy type, response to chemotherapy, overall and progression free survival (OS, PFS) were retrieved. Pearson’s (X2) test, Cox and logistic regression and Kaplan-Meier survival curves were used in statistical analysis. Outcomes and other clinical characteristics of SqCLC were analyzed and compared with other NSCLC. Results: Among 99 NSCLC cases, we identified SqCLC (35.4%), adenocarcinoma (29.3%), undifferentiated (20.2%), large cell carcinoma (12.1%) and adenosquamous carcinoma (3%). Predictors of SqCLC among the whole cohort in univariable and multivariable analyses (MVA) was PS=p<0.033; Odd Ratio 2.54 (95% CI: 1.08-5.99). Among (35) SqCLC cases, median age was 54 years (range: 41-70 years), Male:Female was 4:1. Three-fifth of our cohort were PS >1, nearly 55% were stage III while stage IV represents the remaining. Progressive disease (PD) occurred in 57.1%. Median OS and PFS was 12 and 6 months respectively. Nearly 90% of disease progression were found within 1 year after the chemotherapy onset. There was no difference in median OS or PFS in SqCLC vs other NSCLC (OS= 12 vs 18 months in other NSCLC (p=0.832) while PFS=6 months in both groups (p=0.452). Also, no difference in age (p=0.795) or response to chemotherapy (p=0.689) in both groups. Among SqCLC cohort, poor PS and PD were associated with adverse PFS. However, on MVA, the only predictor was PD (p=0.006, HR=3.06, 95% CI: 1.38-6.79). Median PFS for patients with PS >1 vs =1 was 9 vs 4 months respectively. Median PFS for non-progressive versus PD was 11 vs 4 months respectively (p=0.001, See figure). No difference in survival between stage III and IV (p=0.209). Conclusion: Good PS and chemotherapy responder predict good PFS in SqCLC. In advanced stages; no difference in survival among SqCLC and indeed aggressive treatment is warranted.

Keywords: Squamous cell lung cancer, Advanced stage, National Cancer Institute, overall survival, progression free survival

POSTER SESSION 2 – P2.038 ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/IMMUNOTHERAPY BIOMARKERS – TUESDAY, DECEMBER 6, 2016

P2.038-068 THE DRUGGABLE MUTATION LANDSCAPE OF LUNG ADENOCARCINOMA

Anika Gupta, Caitlin Connelly, Garrett Frationt, Juliann Chmielecki, Siraj Ali, James Suh, Alexa Schrook, Jeffrey Ross, Philip Stephens, Vincent Miller Foundation Medicine, Cambridge/United States of America

Background: Molecularly targeted therapies and immunotherapies have emerged as promising approaches in the fight against advanced-stage cancers, including lung adenocarcinoma. Identifying genomic alterations predictive of targeted therapy response, as well as biomarkers for immunotherapy response, such as tumor mutation burden (TMB), could minimize the utilization of ineffective therapies and help overcome tumor drug resistance, improving patient outcomes. We examined the largest previously described dataset, consisting of genomic alterations of ~10,000 lung adenocarcinoma patients, to characterize the landscape of druggable alterations and identified previously undetected co-occurrence and exclusivity relationships between genomic alterations. Methods: Comprehensive genomic profiling (CGP) based on hybrid capture-based next-generation sequencing of the full coding regions of up to 315 cancer-related genes was performed.
genes was performed on 10,472 lung adenocarcinomas. Base substitutions, indels, copy number alterations and gene fusion/ rearrangements were assessed. TMB was calculated as the number of somatic, coding, base substitutions and indels per megabase of genome examined (high TMB > 20 mutations/Mb). Results: Patient median age was 65 years (range: 13 to 90 years), and 56% were female. The alteration frequencies of the druggable NCCN lung adenocarcinoma guideline genes were: EGFR (20.5%), BRAF (5.8%), ERBB2 (5.7%), MET (5.2%), ALK (4.3%), RET (2.1%), and ROS1 (1.4%). 57% and 2.5% of samples had alterations in zero or multiple of these genes, respectively. Few cases with high TMB were found in samples with alterations in EGFR (3.6%) or ALK (2.6%), while a larger percentage with alterations in BRAF (12.9%) or zero NCCN genes (17.4%) had high TMB. 269 cancer-related genes was performed on 10,472 lung adenocarcinomas. Base substitutions, indels, copy number alterations and gene fusion/rearrangements were assessed. TMB was calculated as the number of somatic, coding, base substitutions and indels per megabase of genome examined (high TMB > 20 mutations/Mb). Results: Patient median age was 65 years (range: 13 to 90 years), and 56% were female. The alteration frequencies of the druggable NCCN lung adenocarcinoma guideline genes were: EGFR (20.5%), BRAF (5.8%), ERBB2 (5.7%), MET (5.2%), ALK (4.3%), RET (2.1%), and ROS1 (1.4%). 57% and 2.5% of samples had alterations in zero or multiple of these genes, respectively. Few cases with high TMB were found in samples with alterations in EGFR (3.6%) or ALK (2.6%), while a larger percentage with alterations in BRAF (12.9%) or zero NCCN genes (17.4%) had high TMB. 269 cancer-related genes was performed on 10,472 lung adenocarcinomas. Base substitutions, indels, copy number alterations and gene fusion/rearrangements were assessed. TMB was calculated as the number of somatic, coding, base substitutions and indels per megabase of genome examined (high TMB > 20 mutations/Mb). Results: Patient median age was 65 years (range: 13 to 90 years), and 56% were female. The alteration frequencies of the druggable NCCN lung adenocarcinoma guideline genes were: EGFR (20.5%), BRAF (5.8%), ERBB2 (5.7%), MET (5.2%), ALK (4.3%), RET (2.1%), and ROS1 (1.4%). 57% and 2.5% of samples had alterations in zero or multiple of these genes, respectively. Few cases with high TMB were found in samples with alterations in EGFR (3.6%) or ALK (2.6%), while a larger percentage with alterations in BRAF (12.9%) or zero NCCN genes (17.4%) had high TMB. 269 cancer-related
and p53 in a responder model and no change in phosphorylated proteins in non-responding models were observed. Pharmacodynamics studies, validation of responders with more mouse replicates, and testing on the remaining models are ongoing and the results will be reported. Conclusion: 60% of LUSC PDG with PIK3CA mutation demonstrate high sensitivity to pan-PI3K inhibitor. Understanding innate resistance mechanisms of PI3K inhibition may provide important insights on tractable targets and therapeutic strategy for LUSC patients with aberrant PI3K pathway.

Keywords: patient-derived xenografts, Lung Squamous cell carcinoma, BKML120, PIK3

POSTER SESSION 2 – P2.03B: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/ IMMUNOTHERAPY BIOMARKERS – TUESDAY, DECEMBER 6, 2016

P2.03B-072 RESISTANCE TO BET INHIBITORS IN LUNG ADENOCARCINOMA IS MEDIATED THROUGH A MYC INDEPENDENT MECHANISM

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1Integrative Oncology, BC Cancer Research Center, Vancouver/Canada; 2 Cancer Research Center, Vancouver/BC/Canada

Background: JQ1 is an inhibitor of the bromodomain and extraterminal (BET) family proteins, which function as important reader molecules of acetylated histones and recruit transcriptional activators to specific promoter sites. BET protein inhibitors have been shown to control the expression of numerous genes involved in cell cycle, cell growth, and cancer. The down-regulation of c-Myc has been linked to JQ1 inhibition in many non-lung cancer cell lines, while reactivation of c-Myc expression, through co-regulation by GLI2 or activation of Wnt signaling, has been shown to induce JQ1 resistance. However, our lab has previously shown that lung adenocarcinoma (LAC) cells are inhibited by JQ1 through a mechanism independent of c-Myc down-regulation, identifying FOSL1 as a possible target in LAC cells. This suggests that the epigenetic landscape of cells from different origins and differentiation states influences response to JQ1. This study aims to identify potential mechanisms regulating resistance to JQ1 in LAC in order to determine if the epigenome affects this process in different cancer types. Methods: LAC cell lines sensitive to JQ1 treatment, H23 and H1975, were passaged with increasing concentrations of JQ1 until the cells were resistant to high doses of the drug. Expression profiles were generated for parental and resistant cells using Affymetrix Human PrimeView Arrays and genes differentially expressed between the states for each cell line were identified and compared across both H23 and H1975 to identify candidate genes. Protein expression was evaluated through Western Blot analysis to confirm gene changes associated with resistance. Results: Initial morphological and western blot analysis showed resistant H1975 cells underwent EMT transition with significant decrease in E-cadherin and increase in Vimentin. Analysis of differentially expressed genes between the parental and resistant pairs identified 101 significantly differentially expressed genes (Benjamini-Hochberg corrected p-value <0.05) common between the H1975 and H23 lines; however, MYC was not significantly altered nor was FOSL1 expression reactivated. Preliminary findings indicate that AXL and SPOCK1 up-regulation in H1975 and H23, respectively, may be driving resistance in each LAC cell line. Conclusion: The discovery and optimization of small-molecule inhibitors of epigenetic targets is a major focus of current biomedical research. We determined that LAC cells, unlike those from other cancers, develop JQ1 resistance through mechanisms independent of c-MYC, suggesting the epigenomic landscape of a cell can influence both sensitivity and resistance to BET inhibitors. Together, this work will lead to the development of more efficient therapies for lung cancer treatment.

Keywords: drug resistance, Non-small cell lung cancer, epigenetics, Target identification

POSTER SESSION 2 – P2.03B: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/ IMMUNOTHERAPY BIOMARKERS – TUESDAY, DECEMBER 6, 2016

P2.03B-074 NSCLC HOMING NANOPARTICLES SELECTIVELY TRANSECT LUNG CANCER

Gregory Holt1, Pirouz Daftarian2
1Pulmonary, Allergy, Critical Care and Sleep Medicine, University of Miami, Miami/ United States of America; 2Ngm Biopharmaceuticals, San Francisco/CA/United States of America

Background: Gene therapy could treat lung cancer by transfecting cancer cells with plasmid DNA encoding the genes of interest. Unfortunately, it is not clinically feasible to perform repetitive intratumoral injections due to the anatomic location of lung cancer. Methods: To circumvent this problem, we created a dendrimer consisting of a fifth generation nanoparticle attached to a peptide with binding specificity for non-small cell lung cancer called NSCLC-NP. Results: NSCLC-NP shows selective binding and transfection of human lung cells in vivo. In vivo, systemically applied NSCLC-NP home to human lung cancer cells growing in RAG2 KO mice and cause expression of the gene encoded by the attached plasmid. Dendrimers can accumulate at tumors without matched normal controls and are cost-intensive to sequence and analyze tumor-normal pairs in clinical settings due to the Enhanced Permeability and Retention effect. Using a cornel model growing human lung cancer cells, NSCLC-NP show binding to human lung cancer cells is based on the lung cancer homing peptide and not the EPR. Conclusion: The NSCLC-NP reagent is a vehicle to cause expression of any gene encoded by the attached plasmid. Dendrimers can accumulate at tumors without matched normal controls and is imperative to explore the possibility of identifying somatic mutations without matched normal control. Methods: To fulfill the need, we firstly carry out the following preparation based on the mutations detected by MuTect: (i) construct a set of 430 white blood cell samples from tumor patients to serve as VirtualControl; and (ii) build MuTectRepeat using variations from 321 tumor samples (blood or tissue). Subsequently, a comprehensive analysis was performed to identify the somatic SNVs from tumor-only testing: (i) call candidate somatic mutations with MuTect using the same parameters as in tumor-normal testing; (ii) pick out the SNPs with the aid of 1000 Genomes Project, ExAC and VirtualControl; (iii) calculate the mean frequency of the SNPs on a specific genomic segment to serves as the expected allele frequency for a germline mutation to occur on the segment; (iv) perform Z test for each candidate variation and calculate the corresponding Z-score; (v) discriminate the somatic variants from background mutations according to the Z-score, My Cancer Genome, VirtualControl and MuTectRepeat. Results: We present SomaticExcavator, a solution for the identification of somatic SNVs using tumor-only NGS-based test that targets 483 cancer-related genes. To evaluate the consistency of SomaticExcavator with classical tumor-normal analysis, 275 tumor-only or tumor-normal tests were conducted separately. It demonstrates that, 74 percent of tumor-only tests achieved 95% or higher concordance with corresponding tumor-normal tests. Conclusion: In summary, the strategy we present here shows power in providing reliable results of somatic SNVs in the absence of matched normal control, which offers a solution for those whose matched normal controls are not available. Furthermore, with the advantage of reducing the cost of somatic variant calling, it has the potential to enlarge the population of cancer patients who can benefit from personalized medicine.

Keywords: targeted sequencing, somatic SNV, tumor-only

POSTER SESSION 2 – P2.03B: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/ IMMUNOTHERAPY BIOMARKERS – TUESDAY, DECEMBER 6, 2016

P2.03B-075 PD-1 PROTEIN EXPRESSION PREDICTS SURVIVAL IN RESECTED ADENOCARCINOMAS OF THE LUNG

Bojan Zaric1, Luka Bricic2, Anna Buder3, Christian Tomuta1, Anita Brandstetter1, Jorun Buresch1, Stefan Trant1, Vladimir Stojic1, Tomi Kovacevic1, Bransilav Perin1, Robert Pirker1, Martin Filipics1
1Clinic for Thoracic Oncology, Institute for Pulmonary Diseases of Vojvodina, Faculty of Medicine, University of Novi Sad, Serbia; 2Institute of Pathology, Medical University of Graz, Graz/Austria; 3Department of Medicine I, Medical University of Vienna, Vienna/Austria

Background: Immune checkpoint inhibitors targeting programmed cell

Keywords: nanoparticles, dendrimers, lung cancer

POSTER SESSION 2 – P2.03B: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/ IMMUNOTHERAPY BIOMARKERS – TUESDAY, DECEMBER 6, 2016

P2.03B-073 HIGH CONCORDANCE OF SOMATIC SNVS BETWEEN TUMOR-ONLY AND TUMOR-NORMAL TESTING: IMPLICATIONS FOR CLINICAL PRACTICE

Xia Ran, Wei Dong, Yang Guo, Xuehong Meng, Licheng Xiao, Xiaomin Li1, Longgang Wei1, Zhi Jiang, Dongmei Lin
1Beijing Novogene Bioinformatics Technology Co., Ltd, Beijing/China; 2Pathology, Peking University Cancer Hospital, Beijing/China

Background: Typically, somatic mutations are detected by comparing sequencing data from tumor and matched normal samples. However, the normal control is not always available in many practical situations. Moreover, it is cost-intensive to sequence and analyze tumor-normal pairs in clinical application, especially when hundreds of genes are targeted. Therefore, it is imperative to explore the possibility of identifying somatic mutations without matched normal control. Methods: To fulfill the need, we firstly carry out the following preparation based on the mutations detected by MuTect: (i) construct a set of 430 white blood cell samples from tumor patients to serve as VirtualControl, and (ii) build MuTectRepeat using variations from 321 tumor samples (blood or tissue). Subsequently, a comprehensive analysis was performed to identify the somatic SNVs from tumor-only testing: (i) call candidate somatic mutations with MuTect using the same parameters as in tumor-normal testing; (ii) pick out the SNPs with the aid of 1000 Genomes Project, ExAC and VirtualControl; (iii) calculate the mean frequency of the SNPs on a specific genomic segment to serves as the expected allele frequency for a germline mutation to occur on the segment; (iv) perform Z test for each candidate variation and calculate the corresponding Z-score; (v) discriminate the somatic variants from background mutations according to the Z-score, My Cancer Genome, VirtualControl and MuTectRepeat. Results: We present SomaticExcavator, a solution for the identification of somatic SNVs using tumor-only NGS-based test that targets 483 cancer-related genes. To evaluate the consistency of SomaticExcavator with classical tumor-normal analysis, 275 tumor-only or tumor-normal tests were conducted separately. It demonstrates that, 74 percent of tumor-only tests achieved 95% or higher concordance with corresponding tumor-normal tests. Conclusion: In summary, the strategy we present here shows power in providing reliable results of somatic SNVs in the absence of matched normal control, which offers a solution for those whose matched normal controls are not available. Furthermore, with the advantage of reducing the cost of somatic variant calling, it has the potential to enlarge the population of cancer patients who can benefit from personalized medicine.

Keywords: targeted sequencing, somatic SNV, tumor-only

POSTER SESSION 2 – P2.03B: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/ IMMUNOTHERAPY BIOMARKERS – TUESDAY, DECEMBER 6, 2016

P2.03B-075 PD-1 PROTEIN EXPRESSION PREDICTS SURVIVAL IN RESECTED ADENOCARCINOMAS OF THE LUNG

Bojan Zaric1, Luka Bricic2, Anna Buder3, Christian Tomuta1, Anita Brandstetter1, Jorun Buresch1, Stefan Trant1, Vladimir Stojic1, Tomi Kovacevic1, Bransilav Perin1, Robert Pirker1, Martin Filipics1
1Clinic for Thoracic Oncology, Institute for Pulmonary Diseases of Vojvodina, Faculty of Medicine, University of Novi Sad, Serbia; 2Institute of Pathology, Medical University of Graz, Graz/Austria; 3Department of Medicine I, Medical University of Vienna, Vienna/Austria

Background: Immune checkpoint inhibitors targeting programmed cell

Keywords: nanoparticles, dendrimers, lung cancer
death protein 1 (PD-1) and programmed cell death ligand 1 (PD-L1) have demonstrated clinical activity in patients with advanced non-small cell lung carcinoma (NSCLC). The ability of PD-1 and PD-L1 immune checkpoint inhibitors remains controversial. We assessed the prognostic value of PD-1 and PD-L1 IHC in patients with completely resected adenocarcinoma of the lung. Methods: We determined protein expression of PD-1 and PD-L1 in formalin-fixed paraffin-embedded surgical specimens of 161 NSCLC patients with adenocarcinoma histology by IHC. We used the EH33 antibody (Cell Signaling) for PD-1 and the E1L3N antibody (Cell Signaling) for PD-L1 IHC. Cut-points of ≥2% PD-1-positive immune cells at any staining intensity and ≥2% PD-L1-positive tumor cells at any staining intensity were correlated with clinicopathological features and patient survival. Results: Positive PD-1 IHC staining in immune cells was observed in 54% of evaluable tumor samples. Positive staining was not significantly associated with any of the clinicopathological features. Positive PD-1 IHC staining was associated with longer recurrence-free and overall survival of the patients. Multivariate Cox proportional hazards regression analyses identified PD-1 to be an independent prognostic factor for recurrence (adjusted hazard ratio [HR] for recurrence 0.58; 95% confidence interval [CI] 0.36 to 0.94; P = 0.026) and death (adjusted HR for death 0.46; 95% CI 0.26 to 0.82; P = 0.008). PD-L1-positive staining in tumor cells was seen in 59 of 161 (37%) cases. Positive PD-L1 IHC staining correlated with KRAS mutation (P = 0.019) and type of surgery (P = 0.01) but was not significantly associated with any of the other clinicopathological parameters. Positive PD-L1 IHC staining was not associated with survival of the patients (adjusted HR for recurrence 0.92; 95% CI 0.58 to 1.47; P = 0.733; adjusted HR for death 0.61; 95% CI 0.34 to 1.07; P = 0.084). Conclusion: Positive PD-1 but not PD-L1 IHC staining is a favorable independent prognostic factor in patients with completely resected adenocarcinoma of the lung.

Keywords: adenocarcinoma of the lung, PD-1, Immune checkpoint inhibitors, Prognostic biomarkers

P2.03B-077 EGFR/ALK+ PATIENT-DERIVED XENOGRAFTS FROM ADVANCED NSCLC FOR TKI DRUG SELECTION & RESISTANCE DEVELOPMENT: THE REAL-PDX STUDY

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Background: Lung cancer patient-derived xenografts (PDX) have been shown to be representative models for individual patient tumors. Theoretically, such models could inform the choice of subsequent lines of therapy, since PDX development, TKI resistance induction, and subsequent drug-screening can be completed before TKI resistance develops in the patient. The goal of Resistance modeling in EGFR and ALK Lung cancer (REAL-PDX) is to develop PDX models for real-time Treatment selection of subsequent lines of therapy in advanced-stage NSCLC patients. Methods: Since August 2015, Princess Margaret Cancer Centre patients with EGFR/ALK+, as well as lifetime never-smoking lung cancer patients with unknown mutation status, were consented to have additional tumor sampling for PDX development during routine or trial-related biopsies. Tumor sufficiency was confirmed prior to implantation. Tissues were combined immunodeficient (NOD-SCID) mice, with successful engraftment defined as propagation beyond first passage; unsuccessful implantations had no palpable tumor after 6 months. Results: 72/82 (88%) approached patients consented; 49/72 (68%) had adequate tumor tissue for implantation (7% stage I/II; 41% IV); 46 adenocarcinoma, 1 squamous carcinoma, and 1 small cell carcinoma (NSCLC). The ability of PD-1 and PD-L1 immunohistochemistry (IHC) to detect protein expression of PD-1 and PD-L1 in formalin-fixed paraffin-embedded tissues

P2.03B-078 MET GENE AMPLIFICATION AND OVEREXPRESSION IN CHINESE NSCLC PATIENTS WITHOUT EGFR MUTATIONS

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Background: The prevalence and clinicopathologic characteristics of MET amplification and overexpression in Chinese patients with non-small cell lung cancer (NSCLC) remain unknown. In this multicenter study, we focus on revealing the frequency and clinicopathologic characteristics of MET amplification and explore the predictive value of MET amplification and overexpression status to survival in Chinese NSCLC patients. Methods: MET amplification was detected by fluorescence in-situ hybridization (FISH) in 791 patients with EGFR wild-type samples. MET protein expression was detected by immunohistochemistry. Results: In total, 8 patients were identified as harboring MET amplification from 791 NSCLC patients with EGFR wild-type. Among these 8 patients, one was with histology of adenocarcinoma and 7 of adenocarcinoma. There was no statistically
significant difference among age, gender, smoking status and histologic type between patients with and without MET amplification. MET amplification was more frequent in advanced stage and solid predominant subtype of adenocarcinoma. MET protein expression was performed in 395 patients and 138 were positive. Patients with MET protein expression positive had an inferior overall survival compared to those without MET protein expression (45.0 months vs 65.8 months; P=0.001). Multivariate analysis revealed that MET expression was independent prognostic factor for poor overall survival (HR=1.97,P=0.017), while, the MET amplification shows weak relevance for overall survival (HR=1.97a,P=0.251). Conclusion: MET amplification was rare in Chinese NSCLC without EGFR mutation, with a prevalence of about 1%. MET expression but not amplification could be an independent prognostic factor for shorter OS among those EGFR wild-type NSCLC patients.

Keywords: non-small cell lung cancer, MET, amplification, Overexpression
Keywords: Gene mutation, Next Generation Sequencer, Molecular target therapy

Background: In the last decade, translational research led to the identification of oncogenic drivers and the successful development of targeted inhibitors.

Today, especially patients with lung carcinoma with a non-squamous histology benefit from targeted inhibition, for example of EGFR, ALK, ROS1, MET. However, in many cases tumor material is limited and does not allow for complete molecular diagnostics or, in a relapse setting, a re-biopsy may not be possible. Thus, reliable and comprehensive detection of genomic alterations by non-invasive means, such as liquid biopsies are required. In addition, repeated analysis of cell-free tumor DNA allows for disease monitoring while, at the same time, displaying the tumor heterogeneity. Methods: At NEO New Oncology we have developed two hybrid-capture based NGS assays, named NEOliquid and NEOminitumour, for the detection of genomic alterations in tissue or blood with high sensitivity and specificity. NEOliquid is specifically designed for detection of genomic alterations from cell-free DNA and NEOminitumour for detection of more than 90 cancer related genes. NEOliquid and NEOminitumour were evaluated in a panel of 39 clinically relevant cancer cell lines, and were shown to detect 13% tumors with elevated AQP11 mRNA expression (6.18±0.55 vs. 4.28±0.77, p<0.001). Increased AQP11 expression was significantly associated with decreased OS. These patients showed lower median survival of 34.47 versus 52.5 months in patients with low AQP11 expression (logrank test p=0.05). Conclusion: AQP11 is the cisplatin non-DSN target that may significantly contribute to the development of resistance. High AQP11 level is a pro-survival factor protecting tumor cells from cisplatin-induced stress. High AQP11 expression associates with lower OS in lung adenocarcinoma patients and with cisplatin resistance in lung cancer cell lines. With further validation, AQP11 level might be a predictor of cisplatin resistance and overall survival in lung cancer.

Keywords: Aquaporin 11, cisplatin, resistance, cancer
EXPRESSION IN STAGE II AND III LUNG ADENOCARCINOMAS

**P2.03B-085 PROGRAMMED CELL DEATH LIGAND 1 (PD-L1) BIOMARKERS –**

**POSTER SESSION 2 – P2.03B: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/IMMUNOTHERAPY BIOMARKERS – TUESDAY, DECEMBER 6, 2016**

Background: For late stage lung cancer (LC) patients few treatment options are at hand and the survival time is very limited, hence novel therapies and associated biomarkers are urgently needed. Erythropoietin-Producing Hepatocellular carcinoma receptor (Eph) tyrosine kinase family and their ligands, Ephrins, drive multiple hallmarks of cancer e.g. proliferation/invasion. The Eph signaling pathways are attractive drug targets due to their dual role in oncogenesis and tumor progression. We analyzed Ephs/Ephrins signaling in LC cells from pleural effusions (PE) to reveal altered kinase pathways and putative BMIs. We also assessed cytotoxicity and kinome alterations in PE tumor cells exposed to targeted agents and chemotherapy in vitro. Methods: Tumor cells purified from PE, assessed for histology, mutation and translocation status (EGFR, KRAS, BRAF and Alk), were grown in vitro. Toxicity of tyrosine kinase inhibitors (TKIs) (e.g. erlotinib, crizotinib, AG1024, AZD9291, dasatinib), EGFR blocker (cetuximab) and/or chemotherapy (e.g. cisplatin, gemcitabine, etoposide) were analyzed after 72 h with the Tox8 assay. Ephs/Ephrins signaling components were studied using western blot, immunoprecipitation and by proximity ligation assay. Mutations and signaling heterogeneity were visualized using padlock probe method. For kinome profiling PathScan RTK signaling antibody array was used. Results: PE isolated tumor cells were identified as adenocarcinoma, squamous cell carcinoma and SCLC and their EGFR, KRAS, BRAF and Alk mutational status determined. High levels of Ephrin-B3 and phosphorylated EphA2 ser 897, previously shown to be instrumental in driving NSCLC proliferation and invasion in vitro, were confirmed and also shown to directly interact, indicating the importance of this signaling event. The G391R mutation in EphA2, which is reported to cause a constitutive activation of EphA2 and to be linked to metastasis, but also mutations in EGFR (G719A, G719S, T790M and L858R) were detected. The PE derived tumor cells were heterogenous in their survival response to TKIs and chemotherapy. However, cells with ALK translocation were sensitive to crizotinib and EGFR (p=0.01), a low N stage (p=0.05), and the presence of necrosis (p=0.05). Multivariate analysis showed that abundant CD8+ lymphocytes (p=0.01), a low N stage (p=0.05), and the presence of necrosis (p=0.05) were associated with PD-L1 positive expression. It also showed that PD-L1 positive expression was associated with longer RFS (p=0.07, hazard ratio 6.21, 96% confidence interval 1.67-23.26). Abundant CD8+ lymphocytes and stage III adenocarcinoma were unfavorable factors for RFS.

Keywords: drug targets, new therapeutics, pleural effusions, Ephs

**P2.03B-086 HIGH EXPRESSION OF PDL-1 CORRELATES WITH PLEOMORPHIC FEATURES IN NON-SMALL CELL LUNG CARCINOMAS**

**POSTER SESSION 2 – P2.03B: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/IMMUNOTHERAPY BIOMARKERS – TUESDAY, DECEMBER 6, 2016**

Background: With immunomodulatory therapy being integrated into treatment regimes for non-small cell carcinoma (NSCLC), we have reviewed our initial experience within the UK in relation to potential access to treatment with pembrolizumab, in order to assess correlation between tumour morphology and staining patterns. Methods: Immunohistochemistry for PD-L1 (HC PIC PD-L1) was performed with the PD-L1 IHC 22C3 pharmDXTM assay (Dako) on cases being considered for treatment. The test was considered
adequate when more than 100 tumour cells were seen microscopically. When adequate, PD-L1 staining was scored as 0%, 1%, >1-4% or >5% positive membrane staining within tumour cells only. PD-L1 staining was considered positive when the score was >5%. In initial cases, it was noticed that there was an increased staining in cases with pleomorphic features, so a separate cohort of 9 resections of pleomorphic carcinomas was additionally assessed. Results: PD-L1 expression was assessed in 72 NSCLC test cases which comprised 19 lung resections, 31 lung biopsies, 11 lymph node biopsies (5 of which were TBNAs), 4 pleural/pericardial tissue (2 from effusions), and 7 other metastatic sites (cores). There were 52 ADC (8 of which were NSCLC-ADC on IHC and 3 of which were invasive mucinous ADC), 7 SQCC (2 of which were NSCLC-SQCC on IHC), one LCC, 2 NSCLC-NE and 4 NSCLC-NOS. 6 cases were inadequate. Of the 65 cases with adequate tissue, 9 cases had pleomorphic features. A score of >50% was found in 78% (7/9) of cases with pleomorphic features with the remainder being 1-4%, compared to 27% (15/56) in those without pleomorphic features (P=0.05) (1-4% vs >2%, P=0.19). 8 of 9 (89%) additional resected pleomorphic carcinomas showed >50% positivity with one case showing 10% positive staining concentrated in the pleomorphic area. Conclusion: Initial data show a correlation between PD-L1 staining and pleomorphic features in non-small cell lung carcinomas. Assessment on cell blocks obtained from TBNAs and effusions also provide assessable material.

Keywords: Immunotherapy, Cancer, PD-L1, pleomorphic

P2.03B-087 PD-L1 EXPRESSION IN ADENOSQUAMOUS LUNG CARCINOMA AND THE COMPARISON WITH THE OTHER COMMON VARIANTS OF NON-SMALL CELL LUNG CANCER

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Background: Adenosquamous lung carcinoma (ASC) is a hybrid tumor made of adenocarcinoma and squamous cell carcinoma in one tumor. It is a rare disease with poor prognosis compared with other common variants of non-small cell lung cancer (NSCLC). There is a persisting need for identifying more effective targeted therapy methods. Immune check point therapy targeted PD-1 or PD-L1 has achieved promising results in advanced stage NSCLC. PD-L1 expression has been suggested as a potential biomarker to tailor patients who will benefit from these treatments. There is limited data regarding the expression of PD-L1 in lung ASC and its correlation with the driver oncogene changes. Methods: Protein expression of PD-L1 was examined by immunohistochemistry method using the VENTANA PD-L1(SP263) Rabbit Monoclonal Antibody. Messenger RNA level of PD-L1 was evaluated by in situ hybridization method. EGFR, K-ras, and B-raf mutation were detected by real time PCR method. Tissue microarrays (TMAs) containing formalin fixed paraffin embedded (FFPE) NSCLC cases were used in this study. Results: This study included 51 cases of lung ASC, 133 cases of lung adenocarcinoma (AD), and 83 cases of lung squamous cell carcinoma (SCC), totally. PD-L1 expression rate in lung AD at the mRNA level and the protein level is highly correlated, which the kappa coefficient of the two examination methods is 0.856 (P=0.000). For the 46 cases of lung ASC, which the glandular and squamous components were analyzed separately, PD-L1 expression were divergent and mainly occurred in the SCC component of lung ASC. PD-L1 expression rate in the SCC component of ASC is similar with the result of lung SCC (39% vs 29%, P=0.327), its expression rate in AD component of ASC is the same with the result of lung AD (13.7% vs 13.5%, P=1.000). There is no association between PD-L1 expression and clinicopathological characters in lung ASC, for example sex, age, smoking status, clinical stage, prognosis, EGFR mutation, K-ras mutation, or B-raf mutation, et al. Conclusion: PD-L1 expression in the two components of lung ASC is divergent and more prone to be expressed in the SCC component. Lung ASC may not be suitable for the PD-L1 targeted therapy because of this divergent expression status.

Keywords: PD-L1, EGFR mutation, non-small cell lung cancer, adenosquamous lung carcinoma

P2.03B-089 CDIC IN LUNG ADENOCARCINOMA: PROGNOSIS AND CELLULAR ORIGIN

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Background: Adaptive immune response is critical for cancer surveillance and elimination. Dendritic cells (DC) arise from a hematopoietic lineage distinct from other leukocytes which play a central role in adaptive immunity. CD1c is expressed in DC, presenting exogenous ligand antigens to T cell receptor to activate “unconventional” T cells. This study aims to evaluate the cellular expression and prognostic value of CD1c. Methods: The study used 5 gene expression datasets: UHN181 (lung adenocarcinoma (ADC), n=128), squamous cell carcinoma (SCC, n=63), GSE30219 (ADC n=81, non-ADC n=138), and 3 integrated cohorts (non-SqCC NSCLC n=1106), PRECOG (39 types of cancer, n=18,000), and TCGA (33 types of cancer, n=11,000). Cancer Cell Line Encyclopedia (CCLE) data were used to determine if CD1c was expressed by cancer cell lines. CIBERSORT algorithm was used to estimate immune cell fraction and Cox proportional hazard models were used to test association of CD1c expression with survival. Immunohistochemistry (IHC) was used to measure protein expression of CD1c. Results: Except for hematopoietic and lymphoid cancer cell lines, all CCLE cell lines lack CD1c expression. CIBERSORT analysis together with Pearson correlation analyses on the ADC cases in UHN181, the integrated cohort, and GSE30219 showed that CD1c was expressed by DC. IHC showed staining with a dendritic cell shape pattern. However, the staining of CD1c did not overlapped with CD11c staining, suggesting a specific DC subtype. Cox proportional regression revealed that CD1c was significantly prognostic in the UHN181 ADC cohort (HR=0.75,
Abstracts

**P.038-090 A CTLA-4 ANTAGONIZING DNA APTAMER WITH ANTI-TUMOR EFFECT**

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Background: The discovery of cytotoxic T lymphocyte antigen-4 (CTLA-4) blockade and its successful clinical translation has revolutionized the concept of cancer immunotherapy. Although immune checkpoint-targeting antibody has shown impressive results in a diverse array of cancers, their cell-based manufacturing process influences production capacity and cause variation between batches. Aptamers are synthetic DNA or RNA oligonucleotides that encompass antibody-mimicking functions. With its chemically synthetic nature, aptamer can be produced in large scale with controllable batch variations and lower manufacturing cost.

Methods: Here, we report the development of a CTLA-4 antagonizing DNA aptamer, termed aptCTLA-4, using the cell-based SELEX and next-generation sequencing.

Results: The aptCTLA-4 exhibits good binding affinity (dissociation constant, 11.8 nM). In vitro lymphocyte proliferation assays demonstrated that the aptCTLA-4 promotes T cell proliferation, and in vivo murine syngeneic tumor models further revealed its tumor-inhibitory effects. Conclusion: Our data suggest the translational potential of the aptCTLA-4 to be developed into a therapeutic aptamer.

Keywords: Immunotherapy, Aptamer, CTLA4, SELEX

**POSTER SESSION 2 – P.038: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/IMMUNOTHERAPY BIOMARKERS – TUESDAY, DECEMBER 6, 2016**

**P.038-091 CD47 PROMOTES TUMOR INVASION AND METASTASIS IN NON-SMALL CELL LUNG CANCER**

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Background: CD47 is overexpressed in many human cancers and its level positively correlates with tumor invasion and metastasis. However, little is known on the expression and biological significance of CD47 in human non-small cell lung cancer (NSCLC). Methods: In this study, we measured the expression level of CD47 in NSCLC tissues and cell lines, and examined its correlation with different clinicopathological parameters. The functional significance of CD47 in NSCLC migration/invasion was analyzed both in vitro and in vivo. The biological importance of Cd424 in this process was evaluated. Results: CD47 was significantly up-regulated in NSCLC cell lines and tumor tissues than in matched tumor-free control tissues. Increased CD47 expression correlated with clinical staging. lymph node metastasis and distant metastasis. To understand the biological significance of CD47, we applied both gain-of-function and loss-of-function approaches in NSCLC cell lines. The siRNA-mediated down-regulation of CD47 inhibited cell invasion and metastasis in vitro, while the overexpression of CD47 by plasmid transfection generated the opposite effects. In vivo, CD47-specific sRNA significantly reduced tumor growth and metastasis. On the molecular level, the expression of CD47 correlated with that of Cd422 both in the cell lines and NSCLC specimens. Inhibition of Cd422 attenuates the invasion and metastasis of CD47-overexpressing cells. Conclusion: Our findings provide the first evidence that CD47 is an adverse prognostic factor for NSCLC progression and metastasis, and thus a promising therapeutic target. Cd422 is a downstream mediator of Cd47-promoted metastasis.

Keywords: non-small cell lung cancer, CD47, metastasis, Cd422

**POSTER SESSION 2 – P.038B: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/IMMUNOTHERAPY BIOMARKERS – TUESDAY, DECEMBER 6, 2016**

**P.038B-092 PREDICTIVE AND PROGNOSTIC EFFECT OF CIRCULATING TUMOR CELLS IN NON-SMALL CELL LUNG CANCER TREATED WITH TARGETED THERAPY**

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Background: We propose a non-invasive, folate receptor (FR)–based circulating tumor cell (CTC) detection approach to interpret treatment response of targeted therapy between baseline and follow-up CTC values and the feasibility whether CTCs as a prognostic factor in advanced NSCLC with EGFR mutation/ALK translocation.

Methods: This was a prospective, unopen-labeled, single-center trial. From July 25, 2015 to March 11, 2016, 308 advanced NSCLC patients were enrolled to quantified CTC level by negative enrichment using immunomagnetic beads in combination with folate receptor–directed polymerase chain reaction (PCR) that allows secondary amplification of tiny amounts of CTCs in 3mL peripheral blood before the start of targeted therapy and after one month, every two months hereafter of treatment. Among whom, 272 NSCLC patients with EGFR mutation (exon 19del mutation: n=135, L858R mutation: n=37), 39 ALK translocation or undefined lung cancer patients. Sequential analyses were conducted to monitor CTC values during therapy and correlate radiological effects with treatment status. Of 272 eligible and evaluable patients received EGFR-TKI, we found that patients harboring lower CTC levels (<20.5) were associated with longer PFS (432days, 95%CI:332.7-541.3) than those with higher CTC levels (>20.5) (PFS: 308days, 95%CI:245.3-370.7; P=0.017). Patients with CTC <20.5 had a DCR of 77.11% compared with 58.43% in CTC ≥20.5 groups (P=0.008), patients with CTC <20.5 had a ORR of 51.20% compared with 33.96% in CTC >20.5 groups (P=0.029). Decreased CTC values correlated well with partial response after one month or three months’ treatment of EGFR-TKI (P=0.0082 and P=0.0023), but not with stable disease (P=0.1843 and P=0.8606). Multivariate analysis showed that CTC level was an independent prognostic factor for PFS (CTC levels:<20.5 vs ≤20.5, hazard ratio, 0.407; P=0.014). Conclusion: The change of CTCs correlated significantly with radiological response. This strategy may enable non-invasive, predictive and prognostic, specific biomarker in patients undergoing targeted therapies.

Keywords: CTC, Gene mutation, non-small cell lung cancer, Targeted therapy

**POSTER SESSION 2 – P.038B: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/IMMUNOTHERAPY BIOMARKERS – TUESDAY, DECEMBER 6, 2016**

**P.038B-093 VALIDATION AND PERFORMANCE OF A STANDARDIZED CTDNA NGS ASSAY ACROSS TWO LABORATORIES**

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Background: Molecular profiling of tumors using circulating tumor DNA (ctDNA) in the blood of cancer patients, as a liquid biopsy, is rapidly becoming established as a useful source of information to aid clinical decision-making when a solid tumor biopsy is not available, or is limited in amount or quality. ctDNA alterations are often found in a small fraction of the total cell free DNA in plasma, and their detection requires specially designed assays that are sensitive and reproducible. Individual hotspot mutations can be
assayed using technologies such as droplet/digital PCR, but multiplexing such assays is limited by the small amount of clinical material. This can be addressed by assays based on next generation sequencing (NGS), to create sensitive panels for ctDNA analysis. For clinical application, it is essential that such NGS assays be standardized and reproducible, both intra- and inter-laboratory. Standardization for tissue-based NGS assays has only recently been implemented, after much discussion. We describe a strategy for validation and standardization of a high sensitivity NGS-based ctDNA assay between two laboratories, based in the US and UK. Methods: The enhanced eTaM-Seq™ assay (eTaM-Seq™TM) uses efficient library preparations and bespoke algorithms to identify cancer mutations within a panel of 34 genes, covering cancer hotspots as well as entire coding regions of selected genes. To ensure the complex process is standardised and controlled, a high level ISO and CLIA quality management system is implemented. To perform analytical validation of this assay, we used reference standards and plasma controls to demonstrate the sensitivity, specificity and quantitative accuracy of this ctDNA analysis platform. Results: We compared performance of the assay between two laboratories, finding a high rate of concordance and reproducibility for the identification of those found in tissue. Median plasma from cancer patients, our assay provides high sensitivity for variants that are present at allele fraction 0.25% or higher in plasma, and retains substantial sensitivity at allele fractions as low as 0.1%. Standard dilution curves of well-characterized reference samples show that the accuracy of the eTaM-Seq™ assay is predominantly limited by stochastic sampling. Analysis of plasma samples from control individuals demonstrates a low false positive rate. Additional data with associated clinical data will be presented.

Keywords: ctDNA, standardized, Concordance, eTaM-Seq

Poster Session 2 – P2.03b: Advanced NSCLC & Chemotherapy/Targeted Therapy/Immunotherapy Biomarkers – Tuesday, December 6, 2016

P2.03b-095 Retrospective Analysis of Correlation between ACEIs/ARBs and Clinical Outcome in Lung Cancer Patients with Bevacizumab-Based Chemotherapy

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Background: Bevacizumab (BEV), a humanized recombinant monoclonal antibody that targets vascular endothelial growth factor, is widely used in cancer treatment. BEV treatment is generally well-tolerated, however, patients who are treated with BEV have an increased risk of developing systemic adverse events, such as hypertension and proteinuria. We generally use angiotensin I-converting enzyme inhibitors (ACEIs) and angiotensin II type-1 receptor blockers (ARBs) as a treatment of these adverse events. This group of drugs has been found to reduce proteinuria and prevent the development of glomerulosclerosis. Additionally, since angiotensin II stimulates neo-vascularization, and thus act as a growth factor for cancer, previous studies have suggested that ACEIs and ARBs might decrease tumor growth and tumor-associated angiogenesis and inhibit metastasis.

In this study, we aimed to investigate the correlation between proteinuria/ hypertension and clinical outcome, and between ACEIs/ARBs use and clinical outcome in lung cancer patients treated with BEV-based chemotherapy.

Methods: We retrospectively reviewed medical charts of patients at Kobe Red Cross Hospital and Kurashiki Central Hospital, Japan (2009-2014 and 2014-2016). The following patient characteristics were collected: sex, age, race, histology, smoking status, performance status, prior treatments, proteinuria status, proteinuria grade, hypertension status, hypertension grade, and use of ACEIs/ARBs. The following endpoints were evaluated: overall survival (OS), progression free survival (PFS), and antitumor response (OR) in the first-, second- and third-line treatments. Proportional hazards models were used to investigate the correlation between ACEIs use (vs. non-use), hypertension use (vs. non-use) and clinical outcome. The correlation between ACEIs use and antitumor response (OR) was also evaluated.

Results: Among 171 patients, 15 patients were excluded because of diabetes mellitus and use of BEV in late lines. Ninety-nine patients were included in the analysis set. Median treated BEV cycles were 7 cycles. Median OS and median PFS were 13 months and 6 months, respectively. During the study, proteinuria was found in 37 patients (57%). Hypertension was found in 81 patients (82%). Thirty-nine patients (39%) were treated with ACEIs/ARBs, 26 patients with other drugs. Univariate analysis showed that younger age, BEV cycles, and ACEIs/ARBs use were significantly associated with longer PFS, not OS. Younger age and BEV cycles were associated with PFS (p < 0.030 and < 0.001, respectively) on univariate analysis, however, proteinuria, hypertension, and ACEIs/ARBs use were not. There was however a trend for the correlation between ACEIs/ARBs use and anti-tumor response (p = 0.082). Conclusion: Our results suggest that BEV-related proteinuria and hypertension were not prognostic markers for lung cancer patients treated with BEV-based chemotherapy. Further accumulation of patients is needed to assess the potential effect of ACEIs/ARBs on anti-tumor effect and PFS.

Keywords: ACEIs/ARBs, bevacizumab, proteinuria/hypertension, Clinical outcome

Poster Session 2 – P2.03b: Advanced NSCLC & Chemotherapy/Targeted Therapy/Immunotherapy Biomarkers – Tuesday, December 6, 2016

P2.03b-096 Utilisation of a Novel 3D Culture Technology for the Assessment of Chemo-Resistance in Non-Small Cell Lung Cancer

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Background: The development of drug resistance is a major cause of treatment failure in cancer patients, including lung cancer patients. Current in vitro models lack the complexity of the in vivo environment and are not able to fully capture the heterogeneity of cancer cells. Therefore, new in vitro models are needed to accurately reflect the clinical situation and identify drug resistant clones.

Methods: The 3D culture technology (3D-OPUS) used in this study is a novel in vitro model that mimics the heterogeneity and heteroclonality of non-small cell lung cancer (NSCLC) xenografts. Cells are cultured in spinning flasks which create a 3D microenvironment by the application of oxygen and nutrient gradients. These gradients cause phenotypic heterogeneity between the sub-populations of the cells, thereby mimicking the heterogeneity and heteroclonality of the tumour. The 3D-OPUS model is able to mimic the tumour microenvironment by the combination of oxygen and nutrient gradients, which leads to heterogeneity between the sub-populations of the cells. The 3D-OPUS model is able to mimic the tumour microenvironment by the combination of oxygen and nutrient gradients, which leads to heterogeneity between the sub-populations of the cells. The 3D-OPUS model is able to mimic the tumour microenvironment by the combination of oxygen and nutrient gradients, which leads to heterogeneity between the sub-populations of the cells.

Results: The 3D-OPUS model was able to accurately reproduce the heterogeneity and heteroclonality of NSCLC xenografts. The model was able to recapitulate the heterogeneity and heteroclonality of NSCLC xenografts. The model was able to recapitulate the heterogeneity and heteroclonality of NSCLC xenografts. The model was able to recapitulate the heterogeneity and heteroclonality of NSCLC xenografts.

Conclusion: The 3D-OPUS model is a novel in vitro model that accurately reflects the heterogeneity and heteroclonality of NSCLC xenografts. The model is able to mimic the tumour microenvironment by the combination of oxygen and nutrient gradients, which leads to heterogeneity between the sub-populations of the cells. The model is able to mimic the tumour microenvironment by the combination of oxygen and nutrient gradients, which leads to heterogeneity between the sub-populations of the cells. The model is able to mimic the tumour microenvironment by the combination of oxygen and nutrient gradients, which leads to heterogeneity between the sub-populations of the cells.

Keywords: Chemo-resistance, Non-Small Cell Lung Cancer, 3D-OPUS model
**Abstracts**

**P2.03B-098 COMPARISON OF DIGITAL PCR, ION PROTON WITH ARMS-PCR IN TUMOR TISSUE AND PLASMA OF NSCLC PATIENTS**

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Background: Deletions in exon 19 and heterozygous mutations (e.g. L858R) in exon 21 are the mutation hotspots of EGFR, which are validated to be sensitive to EGFR-TKI, while exon 20 T790M mutation of EGFR is resistant to EGFR-TKI. A biopsy is needed to characterize EGFR mutation status. However, the amplification-refractory mutation system PCR (ARMS-PCR) is limited to detect mutation frequency below 1%. The QuantStudio 3D Digital PCR (digital PCR) and NGS were new promising techniques for low frequency mutations detection. In current study, we identified the EGFR L858R, T790M mutations detection. In current study, we identified the EGFR L858R, T790M mutations in 27 NSCLC patients using Ion AmpliSeq panel and digital PCR, then compared the detection with ARMS-PCR. Besides, in need of liquid biopsy, we also assessed the concordence between tumor tissue and circulating DNA (ctDNA) in digital PCR platform. Methods: A total of 27 NSCLC patients with stage IIIb/IV were enrolled, paired tumor tissue and plasma (within 7 days before/after tumor biopsy) were collected. ARMS-PCR were provided by hospital. DNA from tumor tissue was sequenced in Ion Proton system with a customized panel based on Ion Ampliseq Colon and Lung Cancer Research Panel and analyzed using digital PCR. The ctDNA was only detected in digital PCR. Mutation frequency was determined and analyzed to reveal the consistency of platforms or sample types. Results: Compared with ARMS-PCR, identification in tumor of 27 patients, all of the corresponding mutation status were identified in Ion Proton and digital PCR, while the specificity is 95.00% and 85.07% respectively. Compared with Ion Proton, digital PCR achieved 100% sensitivity and 89.06% specificity. Ion Proton identified two more T790M mutations, digital PCR identified other six T790M mutations with frequency between 0.1%-3%. For the tumor tissue mutations identified by Ion Proton and digital PCR, the Spearman's rank correlation coefficient showed a strong positive correlation (R=0.9711). In digital PCR platform, plasma had 62.50% sensitivity, 100% specificity and 88.89% concordance with tumor tissue. However, the frequency called in plasma was lower than that of tumor tissue. Plasma in digital PCR had a specificity of 81.25%, specificity of 96.97% and total concordance of 93.95%. Conclusion: This study demonstrated comparable capacity of mutation detection using Proton and digital PCR compared with ARMS-PCR. Digital PCR could identify lower frequency mutations than Ion Proton. The ctDNA showed

**Table 1**

<p>| Significant Prognostic Factors for OS from Start of 1L (ps. 05) in Final Multivariable Model |</p>
<table>
<thead>
<tr>
<th>Variable (Reference)</th>
<th>Level</th>
<th>Hazard Ratio (95%CI)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age Category at first diagnosis (≤65)</td>
<td>&gt;79</td>
<td>2.6 (1.9-3.7)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Country (Germany)</td>
<td>Spain</td>
<td>1.6 (1.2-2.0)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>TNM disease stage (IIIB)</td>
<td>IV</td>
<td>1.6 (1.2-2.1)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>ECOG Score (0)</td>
<td>12+</td>
<td>1.5 (2.1-9.1) 2.8 (2.1-37.7)</td>
<td>&lt;.0001 1000</td>
</tr>
<tr>
<td>Smoking (Never)</td>
<td>Current</td>
<td>Former</td>
<td>2.3 (1.7-3.2) 1.6 (1.2-2.1)</td>
</tr>
<tr>
<td>Malignant Pleural Effusion (No)</td>
<td>Yes</td>
<td></td>
<td>1.3 (1.0-1.5)</td>
</tr>
<tr>
<td>Any Mutation Testing Conducted (No)</td>
<td>Yes</td>
<td></td>
<td>0.74 (0.6-0.91)</td>
</tr>
<tr>
<td>EGFR+ Mutation Test (Negative, Not Tested, Inconclusive)</td>
<td>Yes</td>
<td></td>
<td>0.75 (0.6-0.97)</td>
</tr>
<tr>
<td>Surgery (No)</td>
<td>Yes</td>
<td></td>
<td>0.36 (0.2-0.6)</td>
</tr>
</tbody>
</table>

The analysis included data from 736 1L patients from 168 sites in the four countries, who were followed for a mean of 1.7 years (range: 22 days – 4.6 years) until the most recent visit (29.3%) or death (71.1%). Conclusion: This rich multi-country clinical dataset provides insight into real world patient clinical, demographic, and treatment characteristics prognostic for OS. The results indicate survival worsened for patients who were older, with higher ECOG scores, TNM stage IV, and smokers. Prior surgery and EGFR testing were associated with improved survival. OS was not associated with insurance plan type.

Keywords: Retrospective Medical Chart Review, multivariate analysis, NSCLC, Prognostic factors
strong specificity detection in patients with NSCLC, while it also indicated that the lower frequency in tumor tissue, the less possibility to be detected in plasma.

Keywords: EGFR, Quasitondo 3D digital PCR, ctDNA, Ion Proton

POSTER SESSION 2 – P2.04: MESOTHELIOMA/THYMIC MALIGNANCIES/ESOPHAGEAL CANCER/OTHER THORACIC MALIGNANCIES
Thymic Malignancies Clinical & Translational – TUESDAY, DECEMBER 6, 2016

P2.04-001 A COMPARATIVE ANALYSIS OF LONG-TERM OUTCOME OF THYMOMA BETWEEN VIDEO-ASSISTED SURGERY AND OPEN RESECTION FROM MULTI-CENTER STUDY DATA
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Background: To compare the oncolgic results between video-assisted thoracoscopic surgery and open resection in early and locally advanced thymomas from multi-center study database using propensity score matching analysis. Methods: Data from 1546 participants in the Korean Association for Research on the Thymus were used to analysis for video-assisted thoracoscopic surgery (VATS) versus open resection from January 2003 to December 2013. We performed propensity score matching analysis for the outcomes of video-assisted thoracoscopic surgery versus thoracotomy lung resection (based on age, gender, MG symptom, tumor size, WHO histologic type, receiving neoadjuvant chemotherapy) (Results: We excised the thymoma using VATS in 513 patients, while 1033 patients underwent open procedures. There were not significant differences between the 2 groups for the 5-year overall survival (p=0.61), recurrence-free survival (p=0.25), and complete resection (p=0.38). The operative times, the hospital stay duration, and the chest tube indwelling time were significantly shorter in the VATS group compared to the open group. Median follow-up duration was 50.13 months (IQR 26.61-79.60). The Masaoka-Koga stage was I/II, III in 556/604/384 patients, respectively. We analyzed on the basis of propensity score matching. There were no significant difference in survival rate (p=0.882/0.632/0.597), recur-free survival (p=0.120/0.104/0.488), and R0 resection (p=0.945/0.656/0.007) among 3 groups in multivariable analysis. Conclusion: Patients undergoing VATS thymectomy had shorter the operative time and the hospital stay duration. Moreover, survival rate and recurrence-free survival are equivalent between VATS and open resection. Therefore, video-assisted thoracoscopic surgery is feasible approach for early and locally advanced stage thymoma.

Keywords: minimal invasive surgery, Thymoma, Thymic carcinoma

POSTER SESSION 2 – P2.04: MESOTHELIOMA/THYMIC MALIGNANCIES/ESOPHAGEAL CANCER/OTHER THORACIC MALIGNANCIES
THYMIC MALIGNANCIES CLINICAL & TRANSLATIONAL – TUESDAY, DECEMBER 6, 2016

P2.04-002 THE EFFICACY OF POSTOPERATIVE RADIOTHERAPY AGAINST THYMIC EPITHELIAL TUMORS ACCORDING TO MASAOKA STAGING AND WHO CLASSIFICATION
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Background: Postoperative radiotherapy (PORT) against thymic epithelial tumors is mainly performed based on Masaoka staging. However there is no definite indication for PORT, and its efficacy is still controversial. Meanwhile, the relationship between the efficacy of PORT and WHO classification is also unclear. This study aimed to clarify the efficacy of PORT in association with both Masaoka staging and WHO classification. Methods: A 262 patients with thymic epithelial tumors surgically treated in our institute from April 1990 to December 2015 were reviewed. The clinicopathological data were retrospectively evaluated for prognosis and recurrence. Results: There were 86 patients with stage I, 21 with stage II, 35 with stage III, 13 with stage IVa, 7 with stage IVb thymic epithelial tumors according to Masaoka staging. As for histological type, 37 patients had type A, 50 had type AB, 59 had type B1, 43 had type B2, 44 had type B3, and 29 had type C (thymic carcinoma) according to WHO classification (2004). Eighty cases (30.5%) underwent PORT. Although PORT showed no association with OS (hazard ratio (HR), 0.565; 95% confidence interval (CI), 0.298 to 1.070; p=0.080), there was no recurrence in patients who received PORT. Subgroup analysis of Masaoka staging (stage-II: HR, 2.4; 95% CI, 0.305-6.607; p=0.078, stage III-IV: HR, 0.436, 95% CI, 0.145 to 1.302, p=0.137, or WHO classification (type A-B1: HR, 2.859, 95% CI, 1.050-7.719; p=0.030, type B2-C: HR, 1.460, 95% CI, 0.502 to 4.248; p=0.488) alone showed no association with prognosis either. However in thymoma patients who were classified in both stage-IIIIV and type B2-C group, PORT was associated with better OS (HR, 0.189; 95% CI, 0.049 to 0.724; p=0.05). Conclusion: PORT is effective in patients with thymic epithelial tumors who are classified in both stage-IV and type B2-C.

Keywords: postoperative radiotherapy, WHO classification, thymic epithelial tumor, Masaoka staging

POSTER SESSION 2 – P2.04: MESOTHELIOMA/THYMIC MALIGNANCIES/ESOPHAGEAL CANCER/OTHER THORACIC MALIGNANCIES
THYMIC MALIGNANCIES CLINICAL & TRANSLATIONAL – TUESDAY, DECEMBER 6, 2016

P2.04-003 CHEMOTHERAPY IN ADVANCED THYMIC EPITHELIAL TUMORS: INSIGHTS FROM THE RYTHMIC PROSPECTIVE COHORT
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Background: Thymic Epithelial Tumors (TET) are rare intrathoracic malignancies, which may be aggressive and difficult to treat. In the advanced setting, chemotherapy may be delivered as a primary/induction therapy before subsequent surgery or definitive radiotherapy, and/or as exclusive treatment in patients for whom no focal treatment is feasible, and/or in the setting of recurrences. As no randomized trial and a limited number of prospective studies are available, there is paucity of prospective, multicentre evidence regarding response rates and survival of patients. RYTHMIC is the nationwide network for TET in France. The RYTHMIC prospective database is hosted by the French intergroup (IFCT), and collects data for all patients diagnosed with TET, for whom management is discussed at a national multidisciplinary tumor board (MTB) based on consensus recommendations. Primary, exclusive chemotherapy, and chemotherapy for recurrence accounted for 149 (11%), 37 (3%), and 67 (5%) questions of a total of 1401 questions raised at the MTB between 2012 and 2015. Methods: All consecutive patients for whom chemotherapy and/or systemic treatment was discussed at the RYTHMIC MTB from 2012 to 2015 were identified from the RYTHMIC prospective database. Main endpoints were response rates and progression-free and overall survival. Results: At the time of analysis, data were available for 156 patients (80 thymic carcinomas, and 76 thymomas), for whom the management led to raise 283 questions at the MTB: 67 (24%) for primary chemotherapy, 36 (11%) for exclusive chemotherapy, and 116 (41%) for exclusions. 37 patients received second-line treatment, and 7 patients received third- and fourth-line treatment. In the setting of first recurrence, carboplatin-paclitaxel combination was the most preferred regimen, administered to 54% of patients; overall response and disease control rates to systemic treatments for recurrences were 13% and 42% in thymic tumors, and 19% and 43% in thymomas (p=0.38 and p=0.92, respectively). Median recurrence-free survival after primary chemotherapy was 16.6 months; median progression-free survival after exclusive chemotherapy, and first-, second-, and third-line chemotherapy for recurrence were 6.0 months, and 7.6 months, 6.2 months, and 6.0 months. Conclusion: Our data provide with a unique insight in the efficacy of chemotherapy for advanced thymic epithelial tumors in a real-life setting; our results help the decision-making to better define the optimal therapeutic strategies.

Keywords: chemotherapy, Thymoma, Thymic carcinoma
P2.04-004 THYMECTOMY WITHOUT DEFINITIVE DIAGNOSIS COULD BE FEASIBLE IN PATIENTS WITH SUSPICIOUS OF THYMIC EPITHELIAL TUMOR
Shuhai Hakiri, Koji Kawaguchi, Toshiki Okasaka, Takayuki Fukui, Koichi Fukumoto, Shota Nakamura, Naoki Ozeki, Akira Naoi, Tomoshi Sugiyama, Kohei Yokoi
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Background: As for thymic epithelial tumors (TETs), National Comprehensive Cancer Network guideline has suggested that complete excision of tumor should be performed without preoperative biopsy when resectable. However, there have been very few evidences on this strategy of diagnosis and treatment. The purpose of this study is to evaluate the validity of this strategy in a routine practice setting, and to assess the feasibility and the relevance of the proposed IASLC/ITMIG TNM staging method (Detterbeck et al. J Thorac Oncol 2014;9:S65). Our objectives were 1) to analyze our experience on a consensus statement of ITMIG (Marx et al. J Thorac Oncol 2014;9:596), 2) to assess the diagnostic performance for TETs histologic subtyping, and 2) to assess the diagnostic performance for TETs histologic subtyping, and 2) to assess the diagnostic performance for TETs histologic subtyping, and 2) to assess the feasibility of applying the IASLC/ITMIG TNM staging system when applying the IASLC/ITMIG TNM staging system to patients with suspicious of TETs who underwent thymectomy without biopsy is feasible in patients with suspicious of TETs when they are considered resectable, although there are some tumors such as thymic cyst and MALT lymphoma hard to distinguish from TETs.

Keywords: biopsy, thymectomy, thymic epithelial tumor, thymus

P2.04-008 UPDATED INCIDENCE OF THYMIC EPITHELIAL TUMORS (TET) IN FRANCE AND CLINICAL PRESENTATION AT DIAGNOSIS
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Background: TETs are rare malignancies with an overall described incidence of 0.13 per 100,000 people-years. Given this, most of our knowledge is largely derived from small single-institution series. RYTHMIC (Réseau tumeurs Thymiques et Cancer) is a French network for TET with the objective of territorial coverage by 14 regional expert centers, systematic discussion of patients at national tumor board and collection of nationwide data within a centralized database. We reviewed our activity in 2015 in order to describe the epidemiology and main characteristics at diagnosis of thymic malignancies in France. Methods: Through RYTHMIC, we prospectively collected all patients (pts) with new diagnosis of primary TET in France in 2015. Epidemiologic, clinical, pathologic and surgical data were prospectively collected within a centralized database. Histologic subtype was centrally reviewed according to the WHO classification and stage by modified Masaoka-Koga classification. Results: A total of 234 cases with new diagnosis of primary thymoma (T) or thymic carcinoma (TC) have been discussed at RYTHMIC between Jan to Dec 2015. Among them, 58% were males; median age was 62 years (range 27-80) for males and 61 years for females [range 24-84]; 20% of the pts presented an autoimmune disorder (AI); myasthenia gravis was the most common in 76% of them. History of previous malignancies was described in 15% of the pts, being melanoma, prostate and breast cancer the most frequently observed. Any potentially relevant environmental exposure was declared for most of the pts. Histologic subtype was then classified as follows: A/AB/B1/B2/B3/TC/neuroendocrine tumors and rarely variants in 7% /23% /13% /24% /9% /16% /8% respectively. Stage II-III/IV tumors were observed in 63% /37% respectively. Mediastinal pleural, mediastinal nodes and lung were the most common metastatic sites. A significant correlation was found between histologic sub-type (T vs TC) and presence of AI (p=0.01) and stage (I-II vs III-IV, p=0.004); no significant correlations were seen with gender (p=0.27). Conclusion: The estimated incidence of TETs in France in 2015 is 0.35 per 100,000 persons, based in our activity. The inclusion in the RYTHMIC network is mandatory but is still based on physician’s request. Although we might underestimate the incidence, it seems to be higher compared to other countries’ registries. The high occurrence of previous cancer might underlie variations in environmental or genetic risk factors.

Keywords: TETs, Incidence, France
CT was considered positive for any reported PET avidity as stated in the official report and the reference was the resected specimen reported by histopathology using WHO criteria. Diagnostic test performance was expressed as sensitivity, specificity, positive and negative predicted values with corresponding 95% confidence intervals. Results: Between January 2002 and June 2015 a total of 134 patients were submitted with a mean age (SD) of 55 years (16) of which 69 (51%) were men. All patients had pre-operative PET CT and the histology was thymic hyperplasia in 10 patients (8%), thymic cyst in 8 (6%) and no malignancy in 15 (11%) and these were classified as "benign". Histology was thymoma in 55 patients (44%), other malignancies in 38 (28%) and thymic carcinoma in 8 (6%), and these were classified as "malignant". The sensitivity and specificity of PET/CT to correctly classify malignant disease were 83% (95% CI 74 to 89) and 58% (37 to 78). The positive and negative predictive values were 90% (83 to 95) and 62% (26 to 63). Conclusion: The results of our study suggests reasonable sensitivity but no specificity implying that a negative PET/CT is useful to rule out the diagnosis of malignant disease whereas a positive result has no value in the discrimination between malignant and benign disease of the anterior mediastinum.

Keywords: Anterior mediastinal, diagnostic performance, PET-CT

P2.04-009 TUMOR SIZE DID NOT AFFECT MASAOKA STAGING AS PREDICTORS OF RECURRENCE IN THYMOMA

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Background: This single-institution retrospective study assessed the predictive value of Masaoka stage plus tumor size in predicting thymoma recurrence following resection. Methods: Four models using binary logistic regression were developed for evaluating the relationship of tumor size and Masaoka stage in predicting recurrence. Model I and II included Masaoka stage and median tumor size, respectively. Model III included these two values and their interaction terms (Masaoka stage × median tumor size). Model IV did not include the interaction between the two parameters as it was not significant. Results: Model IV was determined to be the best model as it had the lowest -2LogL and used the least number of included parameters. Using Model IV, Masaoka stage positively correlated with recurrence of thymoma (P = 0.001). The risk of recurrence of the patients with Masaoka stage III-IV was significantly higher than that of patients with Masaoka stage I (OR= 36.17, 95% CI: 4.30-304.48, P = 0.001). However, inclusion of tumor size did not influence the predictive value of Masaoka staging for tumor recurrence (P = 0.137). Conclusion: The data suggest that Masaoka stage plus tumor size is not a better alternative to Masaoka stage alone for tumor recurrence following tumor resection in patients with thymoma.

Keywords: Masaoka stage, thymoma, tumor size
grading was WHO B3 (33%) followed by AB (25%). 58% had surgical margins < 1 mm, with tumour at margin in 24%. 39 patients (51%) had adjuvant radiotherapy, with median follow-up of 5.1 years for these patients. A radiotherapy dose of 45 – 50.4 Gy in 1.8 Gy fractions was used. 5-year survival for the whole cohort was 68% after surgery alone, and 86% with adjuvant radiotherapy, but the difference was not statistically significant. There were no deaths during follow-up in patients who had clear surgical margins, with or without radiotherapy. If surgical margins < 1 mm, there was a trend towards improved overall survival with adjuvant radiotherapy (5-year survival 88%), compared to surgery alone (5-year survival 50%) (log-rank test chi-square 3.7, p = 0.056) (Fig. 1).

![Survival Functions](image)

**Conclusion:** Thymomas had a significantly better prognosis than thymic carcinomas suggesting that these are 2 different disease processes. The variability in treatments received reflects the lack of information and general consensus. Given the rarity of these tumours, greater emphasis must be placed on collaborative efforts, to increase patient numbers and obtain meaningful results that will increase our understanding of this challenging group of patients and improve outcomes.

**Keywords:** Thymoma, Thymic carcinoma

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**P2.04-012 A RISK OF DEATH FROM A SECOND CANCER FOLLOWING COMPLETE RESECTION OF THYMOMA**

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**Kyoto University, Kyoto/Japan**

**Background:** A portion of patients undergoing complete resection of thymoma develop recurrence of thymoma, while those undergoing thymectomy for thymoma are at risk of developing a second cancer, but it remains unknown whether those patients are more at risk of death from thymoma or from a second cancer. Methods: Retrospective chart review was performed on our prospectively maintained database of patients undergoing complete resection of thymoma at our institution between 1991 and 2016. Thymoma-specific survival was calculated from thymectomy to death of recurrence of thymoma. Second cancer-specific survival was calculated from thymectomy to death of a second cancer. Both were estimated with Kaplan-Meier method. Results: Follow-up ranged from 1 to 239 months (median: 54). One hundred and sixty four patients were identified. During the follow-up, there were four thymoma deaths and 4 deaths from a second cancer. Five-year and 10-year thymoma specific survival was 97.8% and 96.1%, respectively. Five-year and 10-year second cancer specific survival was 98.2% and 96.1%, respectively. Conclusion: It appears that patients undergoing thymectomy for thymoma are at a similar risk of a second cancer death to that of thymoma death. However, there are too few events during the follow-up and a multi-institutional database is required to more rigorously evaluate both risks.

**Keywords:** Thymoma, survival, a second cancer

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**P2.04-013 PROGNOSIS FACTORS AND SURVIVAL ANALYSIS IN THYMIC EPITHELIAL TUMORS**

Luis Del Carpio, Margarita Majen, Laura Lopez, Josep Belda, Elisabeth Martinez Tellez, Joan Carles Trujillo, Alfons Torrego, Virgina Pajares, Núria Farré, Enrique Lerma, Valle Camacho, Alejandro Fernandez, Ana Muñoz, Georgia Anguera

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**Background:** Tumours of the thymus are rare and consensus on their management is lacking. We aimed to assess outcomes of patients diagnosed over the last 11 years. Methods: We identified all patients diagnosed with thymic tumours in Northern Ireland between January 2004 and December 2015 as recorded in the Cancer Registry. Electronic Care Records were used for data collection. Results: Fifty-seven patients were identified, including 9 thymic tumours in Northern Ireland between January 2004 and December 2015. Of these patients, 44 thymomas, 3 neuroendocrine tumours and 1 with small cell features. Mean age at diagnosis was 62 (16-82) and 26% presented with paraneoplastic phenomena. Of the thymoma patients, the majority presented later, with > 75% with stage 3 or 4 disease. The variability in treatments received reflects the lack of information and general consensus. Conclusion: The long-term outcomes of thymic epithelial tumours are excellent after complete surgical excision. There is a trend towards improved overall survival with adjuvant radiotherapy in patients with surgical margins less than 1 mm. Routine referral of patients with close surgical margins for consideration of radiotherapy is recommended.

**Keywords:** Radiotherapy, Thymoma, thymectomy
Background: Thymic epithelial tumors (TET) include thymomas (T) and thymic carcinomas (TC). TET are rare malignant tumors usually associated with paraneoplastic syndromes (PNPs). The objective of the study is to describe our experience and to analyze the prognostic factors. Methods: Retrospective analysis of the clinical and pathological characteristics of 42 patients (pts) diagnosed with TET in our institution from 1990 to 2016. We analysed the outcomes in terms of progression-free survival (PFS) and overall survival (OS) and their association with clinical factors: age, performance status, presence of PNPs, TNM stage, WHO classification, complete resection and treatment. Kaplan Meier method and Cox regression were used. Results: Mean age: 55 years (27-86). 19 (45.2%) women. First treatment: surgery in 34 pts (81%) and platinum based chemotherapy in 6 pts (14%). 2 pts (5%) were untreated. 14 pts (41%) received postoperative radiotherapy. WHO classification: 6 pts (14.3%) type A, 12 (28.6%) AB, 3 (7.1%) B1, 7 (16.7%) B2, 7 (16.7%) B3 and 3 (6.7%) C. TNM staging: 20 pts (48.8%) stage I, 4 (9.8%) stage II, 6 (16.6%) stage III and 9 (22%) stage IV. 25 pts (59.5%) had PNPs at diagnosis: 21 (50%) myasthenia gravis, 2 (4.75%) aplastic anemia and 2 (4.75%) others. The presence of PNPs were associated with better OS than those without PNPs (236m, 95% CI 147-448 vs 66.5m, 95% CI 1.3-131.7m, p=0.006, HR 0.76, p=0.026 ) and also with early diagnosis (stage I for pts with PNPs 56% vs 42% without PNPs). In the multivariate analyses, only C type remained statistically significant (HR:13.5, p=0.024). No differences were found when using TNM classification or complete resection. Conclusion: Patients with C type TET had worst prognosis. The presence of a PNP is associated with better OS possibly due to and early diagnosis.

Keywords: Thymoma, thymic carcinoma, thymoma, Paraneoplastic syndromes

POSTER SESSION 2 – P2.04 - MESOTHELIOMA/THYMIC MALIGNANCIES/ESOPHAGEAL CANCER/OTHER THORACIC MALIGNANCIES
THYMIC MALIGNANCIES CLINICAL & TRANSLATIONAL – TUESDAY, DECEMBER 6, 2016

P2.04-014 RETROSPECTIVE STUDY OF PLEUROPNEUMONECTOMY FOR THYMOMA WITH DISSEMINATION
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Background: We usually perform a chemotherapy for thymoma with dissemination. But it was reported that reduction of thymoma was provided good long term survival. Methods: we reviewed retrospectively pleuropneumonectomy for thymoma with dissemination to determine the benefit. From 1996 to 2015, there were 172 patients with thymoma underwent. Of 172 patients, there were 4 patients with pleuropneumonectomy for thymoma with dissemination. Results: 4 patients were all male. The previous treatment were included the operation, chemotherapy, and chemo-radiation therapy. Two patients were Masaoka I, and two patients were Masaoka IV. Two patients were with MG. Two patients underwent right pleuropneumonectomy. The complications after the operation were bleeding, cardiac herniation, bronchial fistula, empyema. All patients were alive (from 18 month to 86 month), but two patients have recurrence, vertebra and retroperitoneum. Conclusion: We revealed that pleuropneumonectomy for thymoma with dissemination is a high morbidity rate. However pleuropneumonectomy may provide good long term survival. It is important that the selection of patient for example young male, good performance state.

Keywords: Thymoma, pleuropneumonectomy

P2.04-016 IS FDG-PET USEFUL FOR DISTINGUISHING BETWEEN THYMIC EPITHELIAL TUMORS AND MALIGNANT LYMPHOMA
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1Department of Thoracic Surgery, Keio University, School of Medicine, Tokyo/Japan, 2Pathology, Keio University School of Medicine, Tokyo/Japan

Background: It is difficult to diagnose the tumor in the anterior mediastinum by computed tomography. Distinguishing between thymic epithelial tumors and malignant lymphoma is important, because therapeutic strategy is difficult in each disease. The objective of this study was to clarify the usefulness of positron emission tomography (PET) using 18F-fluorodeoxyglucose (FDG) for distinguishing thymic epithelial tumors and malignant lymphoma. Methods: We retrospectively reviewed FDG PET-CT scans of 42 patients pathologically diagnosed by surgery or biopsy as thymic epithelial tumors or malignant lymphoma. FDG uptake was measured at the maximum standard uptake value (SUVMax). Student t tests were used to assess association between SUVMax and pathological diagnosis. Results: Among the 42 patients, 26 patients had a pathological diagnosis of thymoma: WHO classification type A in 3 patients (11%), type AB in 5 patients (19%), type B1 in 10 patients (19%), type B2 in 11 patients (26%), and type B3 in 2 patients (7%). Eight patients had the thymic carcinoma. Eight patients had the malignant lymphoma. The SUVMax in malignant lymphoma (13.4±6.3) was significantly higher than that in the thymoma group (4±2.8) (p<0.001). The SUVMax in thymic carcinoma (7.9±3.0) was higher than that in the thymoma group (4±2.8) (p<0.001). Conclusion: FDG PET-CT is helpful for distinguishing malignant lymphoma from thymic epithelial tumors with cut-off value of 7.3.

Keywords: Thymoma, FDG PET-CT, Thymic carcinoma, malignant lymphoma

P2.04-015 THYMOMA AND THYMIC CARCINOMA - OUR EXPERIENCE
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Background: Thymoma is most frequent epithelial neoplasm of mediastinum. It represents around 20% of primary mediastinal masses and occurs most frequently in the age of 40-60 years, affecting equally both men and women. WHO classification separates thymoma into A, AB, B1-B3 subtypes, a term ‘thymoma C’ is usually used for thymic carcinoma. Paraneoplastic symptoms may accompany thymoma frequently. Prognosis of thymoma is variable, with 5-years survival varying according to Masaoka stage (stage I 95±100%, stage IV 25%). Thymoma C represents high-grade malignancy with aggressive behavior and 5-year survival around 30% (all stages). Methods: Present study shows five year follow up of the thymoma series from our department. 35 cases of this tumour were collected, 22 patients were eligible for complete evaluation, including history, Masaoka stage, first- and second-line treatment, overall survival (OS) and presence of paraneoplastic symptoms. Results: Average age of patients was 59 years, median 61 years (17 women, 18 men). Out of 35 patients, 22 was further evaluated. Thymoma B1 subtype was most frequent (n=9/22). 1-year survival was 83% resp. 53% (operable stages I-II resp. inoperable stages III-IV), 5-year survival was 63% resp. 20%. However, in group of inoperable patients, only three patients (n=3/8) died because of disease progression, with cardiac/coronary disease being most frequent cause of mortality. Highest percentage rate of paraneoplastic symptoms was detected at thymoma B2 subtype: 100% (n=4/4), with overall frequency of paraneoplastic symptoms 45% (n=10/22). Hematological abnormalities were present in 27% (n=6/22) patients (pure red cell anemia, lymphocytosis, agranulocytosis, trombocytopenia), myasthenia gravis 2 (4.75%), aplastic anemia and 2 (4.75%) others. The presence of PNPs and OS according to WHO classification:

<table>
<thead>
<tr>
<th>WHO C</th>
<th>WHO A, B1, B2, B3</th>
<th>p value</th>
<th>HR (univariate)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS (months)</td>
<td>21.2 (8-36.7)</td>
<td>89.3 (69.1-109.6)</td>
<td>0.03</td>
<td>3.12</td>
</tr>
<tr>
<td>OS (months)</td>
<td>66.5 (0-157.5)</td>
<td>296 (98.6-453.3)</td>
<td>&lt;0.001</td>
<td>20.2</td>
</tr>
</tbody>
</table>

The presence of PNPs were associated with better OS than those without PNPs (236m, 95% CI 147-448 vs 66.5m, 95% CI 1.3-131.7m, p=0.006, HR 0.76, p=0.026 ) and also with early diagnosis (stage I for pts with PNPs 56% vs 42% without PNPs). In the multivariate analyses, only C type remained statistically significant (HR:13.5, p=0.024). No differences were found when using TNM classification or complete resection. Conclusion: Patients with C type TET had worst prognosis. The presence of a PNP is associated with better OS possibly due to and early diagnosis.

Keywords: Thymoma, thymic carcinoma, thymoma, Paraneoplastic syndromes

P2.04-017 PROGNOSTIC RELEVANCE OF PD-1/PD-L1 PATHWAY IN THYMIC MALIGNANCIES WITH COMBINED

Abstracts Journal of Thoracic Oncology  •  Volume 12 Issue S1 January 2017
IMMUNOHISTOCHEMICAL AND BIOMOLECULAR APPROACH
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Background: Recent studies on cancer active immunotherapy showed the effectiveness of blockade of PD-1/PD-L1 pathway in several tumors. The present study evaluated PD-1 and PD-L1 protein expression in thymic epithelial tumors (TETs) in order to improve our knowledge about immune system influence in TETs pathogenesis and natural history and to encourage new therapeutic approach with immunomodulating agents. However, considering the potential bias related to immunohistochemical technique (IHC), we aimed to confirm the PD-1 and PD-L1 immunohistochemical analysis results with a molecular assay. Methods: PD1 and PD-L1 immunohistochemical staining, using BMS PD-L1 (clone 28-8) assay from Dako, and mRNA expression by RT-PCR were evaluated on 68 tissue microarray (TMA) samples (63 thymomas and 5 thymic carcinomas) of patients who underwent surgery for TETs in our institution between 1993 and 2013. Results: PD1/MF ratio was 33/35, median age was 60.5 years (range 21-81). 20 patients presented with Myasthenia Gravis, while 4 experienced other syndromes. All the patients underwent radical surgery (thymectomy) and in the half cases patients underwent a previous biopsy. Out of the 63 thymomas, 27% were AB, 6% B2, 18% A, 6% B1 and 19% B3, 5% were mixed B1-B2 and 19% mixed B2-B3, according to WHO classification. Approximately 56% of the patients had large tumors (>5 cm). According to Masaoka-Koga staging, 41% patients presented pathologic stage IIA, whereas 11%, 29%, 10%, 5%, 4% were found to have stages I, III, IVA and IVB, respectively. PD-L1 mRNA tumor expression was significantly associated with worse prognosis in patients with a tumor diameter >5 cm (HR: 5.40 CI 95% 1.9-78.1, p=0.0083). In particular, median OS was 82 months in patients with simultaneous PD-L1 immunostaining (>1%) and PD-L1 mRNA expression compared to not reached median OS of patients with simultaneous PD-L1 negative IHC and not expressed PD-L1 mRNA (p=0.0178). Furthermore in this patients’ subgroup the age > 60 years was associated with worse prognosis (102 vs. 197 months, p=0.0395). Finally, patients with simultaneous PD-L1 negative IHC and not expressed PD-L1 (>1%) and PD-L1 mRNA expression compared to not reached median OS of patients with simultaneous PD-L1 negative IHC and not expressed PD-L1 mRNA (p=0.178). CNA analysis. We extracted some candidate genes, but farther validations are needed. Conclusion: We reported the results of genome wide gene expression and CNA analysis. We extracted some candidate genes, but further validations are needed.
Keywords: Thymic Epithelial Tumors, PD1-L1, Microarray

Abstracts Journal of Thoracic Oncology • Volume 12 Issue S1 January 2017

P2.04-018 COMPREHENSIVE COPY NUMBER ALTERATION AND GENE EXPRESSION ANALYSIS OF SURGICALLY RESECTED THYMIC CARCINOMA
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Background: Thymic carcinoma is rare and comparatively poorly prognostic. Due to its rarity, our knowledge of treatments and prognostic biomarkers available for these tumors is limited. Previous reports revealed low genetic mutation frequency of the tumors, and the inverse correlation between the frequency of genetic mutation and copy number alteration (CNA). Based on these reports, we hypothesized tumorogenicity of thymic carcinomas is mostly caused by copy number and transcriptional alterations. To substantiate the hypothesis, we extracted and analyzed CNA and gene expression data from surgical samples to elucidate driver genes, druggable targets and prognostic factors. Methods: Between January 2009 and March 2016, patients underwent surgery for thymic epithelial tumor in our institution were reviewed. RNA and DNA of the tumors were extracted from FFPE operative samples, gene expression data were obtained by GeneChip Human Transcriptome Array 2.0 (affymetrix), and CNA were detected by OncoScan (affymetrix). These results were analyzed using Transcriptome analysis console (affymetrix) and Nexus expression for OncoScan (BioDiscovery). Uregulated genes in copy number gained region and down regulated genes in copy number lost region were selected as a candidate of tumorogenesis of thymic carcinoma. Results: We had 10 thymic squamous cell carcinoma samples. As a comparison, we use three samples of type A thymoma. CNA data from thymic squamous cell carcinoma showed similar characteristics, chromosome 1q gain, 6p and q loss, and 16q loss, corresponding with previous reports. Gene expression analysis of thymic carcinoma in comparison with type A thymoma revealed down regulation of the genes, BRD2, HSP90AB1, FOXO3, and MARCKS in chromosome 6, and MTS51 in chromosome 16q.
Conclusion: We reported the results of genome wide gene expression and CNA analysis. We extracted some candidate genes, but further validations are needed.
Keywords: Thymic Carcinoma, Copy Number Alteration, Gene Expression, Microarray

Poster Session 2 – P2.04: MESOTHELIOMA/THYMIC MALIGNANCIES/ESOPHAGEAL CANCER/OTHER THORACIC MALIGNANCIES
THYMIC MALIGNANCIES CLINICAL & TRANSLATIONAL – TUESDAY, DECEMBER 6, 2016

P2.04-019 A PERIPHERAL IMMUNE SIGNATURE ASSOCIATED WITH CLINICAL ACTIVITY OF SUNITINIB IN THYMIC CARCINOMA
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Background: We have previously reported an objective response rate of 26% and disease stabilization in 65% of patients with advanced thymic carcinoma (TC) treated with the multitkiase inhibitor sunitinib after failure of platinum-based chemotherapy. The current study investigates the impact of sunitinib on systemic immunity in patients with thymic epithelial tumors with an aim...
to analyze and interpret immunohistochemical staining results for PD-L1 and PD-1 expression in thymoma and thymic carcinoma (TC) specimens. This study aimed to explore the significance of PD-1 and PD-L1 expression in predicting clinical outcomes and therapeutic responses in patients with TET.

Several key findings were derived from the analysis:

1. PD-L1 expression was detected in 57% (26/35) of samples, including 33% (1/3) of thymic carcinoma pts and 81% (26/32) of thymoma pts. PD-1 expression was detected in 77% (26/35) of tumor samples, including 100% (3/3) of thymic carcinoma pts.

2. PD-L1 expression was significantly associated with lower grade tumors (p = 0.031), but not with overall stage at diagnosis, smoking, recurrence, or diagnosis of myasthenia gravis.

3. A nonsignificant trend towards poorer overall survival was seen in patients with PD-L1 expression (p = 0.097, log-rank test). Unlike prior studies, PD-L1 expression did not significantly associate with stage at diagnosis, smoking, recurrence, or diagnosis of myasthenia gravis.

4. Conclusion: This study confirms high expression of PD-L1 and PD-1 in TET, including thymoma and thymic carcinoma. PD-L1 expression was associated with a trend towards shorter overall survival. The high proportion of patients with high PD-L1 and PD-1 expression supports the use of anti-PD-1 and/or PD-1 antibodies in patients with advanced TET.

Keywords: Thymoma, Thymic carcinoma, PD-1, PD-L1, Oncology, Clinical trials
gene mutation. TET. Masaoka stage and histological subtypes predict the survival of TET. (P = 0.352). Conclusion: Hotspot gene mutations are rare in TET. PIK3CA and B3 thymomas and thymic carcinoma, respectively (P = 0.012). No survival differences were found among patients with stage I, II, III, and IV (P < 0.001). The 5-year survival rates were 100%, 100%, 77.7% in all patients. The 5-year survival rates were 100%, 89% and 75% for good, moderate and poor risk groups, respectively (P = 0.08). There were a significant differences for Masaoka stage (I-II vs III-IV, P = 0.015, p < 0.001), R0 resection (present vs absent, p = 0.06, p = 0.05), histology (thymoma vs TC, P = 0.02, p = 0.01) and prognostic risk groups (good vs moderate vs poor, p = 0.03, p = 0.004) in terms of OS and DFS, respectively.

Conclusion: In our study, prognostic risk stratification was seen to be an important predictor for survival. The patients with TC was stage III-IV at diagnosis and moderate or poor risk groups indirectly and survival rates was found to be less than thymoma.

Keywords: Thymic epithelial tumors, Radiotherapy, survival, prognostic groups

P2.04-023 RARE FREQUENCY OF GENE VARIATION AND SURVIVAL ANALYSIS IN THYMIC EPITHELIAL TUMORS
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Background: Thymic epithelial tumor (TET) is a rare mediastinal neoplasm and little is known about its genetic variability and prognostic factors. This study investigated the genetic variability and prognostic factors of TET. Methods: We sequenced 22 cancer-related hotspot genes in TET tissues and matched normal tissues using Ion Torrent Ampliseq next-generation technology. The panel was used to analyze 1800 mutational hotspots and targeted regions in 22 genes: EGFR, KRAS, BRAF, PIK3CA, AKT1, ERBB2, PTEN, NRAS, STK11, MAP2K1, ALK, DDR2, CNOT1, MET, TP53, FBXW7, FGFR3, NOTCH1, ERBB4, FGFR1 and FGFR2. Overall survival (OS) was evaluated using Kaplan-Meier methods and compared with log-rank tests. Results: A histological analysis of 52 patients with a median age of 52 years old showed that 21 patients (40.4%) were thymic carcinoma, 5 patients with type A thymoma (9.6%), 8 with type AB (15.4%), 6 with type B1(11.5%), 9 with type B2 (17.3%) and 9 with type B3 thymomas (17.3%). Pathological stages at diagnosis included: 18 patients with stage I, 11 patients with stage II, 13 patients with stage III, and 10 patients with stage IV disease. Three gene mutations were identified, including two with PIK3CA mutation, and one with EGFR mutation. The 3 patients with mutation included two cases of thymoma (one with EGFR and the other with PIK3CA mutation) in addition to a case of thymic carcinoma (PIK3CA mutation). The 5-year survival rates were 77.7% in all patients. The 5-year survival rates were 93.3%, 100%, 76% and 22% corresponding to Masaoka stages I, II, III, and IV (P < 0.001). The 5-year survival rates were 100%, 100%, 83.3%, 88.9%, 65.6% and 60.9% in the histological subtypes of A, AB, B1, B2, and B3 thymomas and thymic carcinoma, respectively (P = 0.012). No survival difference was found between patients with and without gene mutation (P = 0.325). Conclusion: Hotspot gene mutations are rare in TET. PIK3CA and EGFR mutations represent candidate driver genes and treatment targets in TET. Masaoka stage and histological subtypes predict the survival of TET.

Keywords: next-generation sequencing, Prognosis, Thymic epithelial tumors, Gene mutation

P2.04-025 RECOMBINANT HUMAN ENDOSTATIN AND/OR CISPLATIN IN TREATMENT OF MALIGNANT HYDROTHORAX AND ASCITES: A MULTICENTER RANDOMIZED STUDY
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1PLA Cancer Center, The Affiliated 81 Hospital of PLA, Nanjing/China, 2Thoracic Oncology, Jilin Provincial Cancer Hospital, Changchun/China, 3Nantong Cancer Hospital, Nantong/China, 4Jinan Military General Hospital, Jinan/China, 5Shanghai First People Hospital, Shanghai/China, 6Anhui Provincial Hospital, Hefei/China, 7Fudan University Shanghai Cancer Center, Shanghai/China, 8Shanghai Pulmonary Hospital, Shanghai/China, 9Beijing Cancer Hospital, Beijing/China, 10Tangdu Hospital, Xi'an/China.

Background: To evaluate the clinical efficacy and safety of intra-pleural injection of recombinant human endostatin (Endostar) and/or Cisplatin in treatment of malignant hydrothorax and ascites. Methods: A total of 317 patients with more than moderate amount of pericardial effusion, malignantly hydrothorax and ascites were randomly divided into group A (Endostar group, n=105), group B (Cisplatin group, n=104) and group C (Endostar combined Cisplatin, n=108). After puncture and drainage, Endostar, 45 mg per time by intra-thoracic injection or 60 mg per time by intra-peritoneal injection was performed in Group A. Cisplatin, 40 mg per time by intra-pleural injection on day 1, 4 and 7, was administrated in group B. Group C was administrated with combined therapy of Endostar and Cisplatin. Results: A total of 317 patients were included in full analysis set (FAS), and 275 patients were included in per-protocol set (PPS). There were 298 cases and 273 cases qualified for evaluation on drug efficacy in FAS and PPS respectively. There was a significant difference in ORR among three groups (P<0.05), and ORR was higher in Group C than that in Group A and B (P<0.05 or P<0.01). Patients without intra-pleural treatment history, with hydrothorax, female, without systemic chemotherapy, with initial treatment on effusion, with sufficient drainage, with hemorrhagic effusion and without diagnosis of gastric carcinoma had better outcome in ORR after treatment (P<0.05 or P<0.01). In those with hemorrhagic effusion, the ORRs in Groups A and C were significantly higher than that in Group B (P<0.01). The median TTP was 68.869 d, 44.951 d, 69.030 d in Groups A, B and C, respectively, with a significant difference (P<0.01), and was shorter in Group B than that in

Keywords: Liver Metastasis, Brain metastasis, Thymic epithelial tumors, survival

P2.04-025 RECOMBINANT HUMAN ENDOSTATIN AND/OR CISPLATIN IN TREATMENT OF MALIGNANT HYDROTHORAX AND ASCITES: A MULTICENTER RANDOMIZED STUDY

POSTER SESSION 2 – P2.04: MESOTHELIOMA/THYMIC MALIGNANCIES/ESOPHAGEAL CANCER/OTHER THORACIC MALIGNANCIES
Esophageal Cancer and Other Malignancies – TUESDAY, DECEMBER 6, 2016
Groups A and C (P<0.05 or P<0.01). The proportion of patients with improved QOL and KPS in Group A was higher than that in Groups B and C after third and sixth administration, respectively (P<0.05 or P<0.01). The incidence of adverse reactions was lower in Group A than that in Group B (P<0.05).

Conclusion: Intra-pleural injection of Endostar is potentially effective in improving the quality of life and overall survival of patients with malignant hydrothorax, with no significant different adverse events comparing with groups A and B. This result is encouraging for further clinical efficacy studies with larger sample size.

Keywords: Recombinant human endostatin, Malignant hydrothorax, Malignant ascites, Endostar

P2.04-026 EXPRESSION PATTERNS OF PD-L1 IN ESOPHAGEAL ADENOCARCINOMAS: COMPARISON BETWEEN PRIMARY TUMORS AND METASTASES

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Background: Immune checkpoint inhibition through PD-L1 (Programmed cell death-ligand 1) is a powerful therapeutic option for many solid tumors, potentially including esophageal adenocarcinomas (EAC). Immunohistochemical expression analysis of PD-L1 may be helpful for guiding therapeutic decisions, but testing may be influenced by heterogeneous staining patterns within tumors and expression changes during metastatic course. Methods: We investigated PD-L1 expression in EAC using tissue microarrays from 116 primary resected tumors, corresponding lymph nodes (n=56) and distant metastases (n=18). PD-L1 expression was analyzed using two different antibodies (SP424 and EILN3), together with intratumoral CD3+ and CD8+ T-cells (TIL counts). In addition, preoperative biopsies and full slide sections from a subset of tumors (n=24) were investigated. Results: PD-L1 expression was first scored as 0%, >0-<1%, >1%, >5%, >50% positive membranous staining of tumor cells and of tumor associated inflammatory infiltrates and/or stroma cells. There was a significant correlation between the results of full slide sections and 12 cores/tumor containing TMA sections (p=0.001), but not with the corresponding biopsies. For further analysis, PD-L1 positivity was defined as >1% positive staining for tumor cells and/or inflammatory and stroma cells according to the majority of current drug trials. We observed a very good concordance between the two antibodies for overall staining (p=0.001), concordance rate 89.5%. SP424 appeared slightly superior in terms of a more homogenous staining pattern. PD-L1 expression in tumor cells was detected by SP424 in 3 cases (2.6%) of primary EAC, whereas expression in the inflammatory and stromal cells was observed in 35 cases (30.2%). PD-L1 positive tumors had higher CD3+ and CD8+ TIL counts (p=0.001 and p=0.001) but no other distinct pathological or clinical features. Of note, there was a significant correlation between tumor PD-L1 expression in primary tumors and lymph node and distant metastases. Conclusion: EAC show tumoral PD-L1 expression only a minority of cases, whereas PD-L1 positivity in the inflammatory and stromal cells can be detected in a significant subset of cases. For the determination of PD-L1 status, it should be taken into account that PD-L1 expression in metastases may differ from primary tumors. Moreover, investigation of superficial small biopsies may produce false staining results, which, however, may be more likely be due to fixation artifacts or vicinity to ulceration than to intratumoral heterogeneity.

Keywords: Esophagus, PD-L1, Cancer, Immunohistochemistry

P2.04-027 TARGETING ADENOSINE A2B RECEPTOR FOR MODULATION OF TUMOR MICROENVIRONMENT, PRIMARY TUMOR GROWTH, AND LUNG METASTASIS

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Background: Adenosine A2A receptor antagonists (A2A-AR ) modulate the tumor microenvironment (TME) and reduce tumor growth. However, clinical development of A2A-AR antagonists has been hampered by lack of robust preclinical models that recapitulate known mechanistic effects of A2A-AR antagonism. Here we describe a novel mouse model that is fully capable of addressing these biological questions through in vivo EPR monitoring of the primary TME that allows simultaneous measurements of tumor pH, and inorganic phosphate (Pi) levels, which are parameters implicated in tumor metastasis and demonstrates how the TME contributes to metastatic spread. In combination, we employ an in vivo immune tumor cell imaging platform in which mice are fitted with cutaneous window chambers containing syngeneic lung tissue transplant to create a lung metastatic site in which differentially-labeled tumor and immune subsets will be imaged via multiphoton microscopy. Results: Our EPR methodology accurately monitors TME changes that occur with tumor growth as well as their modulation by pharmacological inhibition of the A2A-adenosine receptor, giving reason to the use of specific A2A-receptor inhibitors as anti-tumor and anti-metastatic therapeutics. A2A inhibition prevented the accumulation of Pi in the tumor interstitial space for every tumor model tested, which includes lung adenocarcinoma, breast adenocarcinoma, colon carcinoma, and melanoma. The exact role this plays in tumor initiation and progression is not completely elucidated but correlates with the reduction of tumour lung metastases and tumor growth. Secondly, our window chamber model enables spatiotemporal analysis of pre-metastatic niche enrichment, individual tumor cell recruitment, and subsequent secondary tumor growth with specific focus on metastatic lung disease. To our knowledge, no model exists capable of unifying these aspects of tumor biology and immunity. Conclusion: The project will lead to understanding a key process of metastasis and thus allow targeted immunotherapeutics and/or combinations to block metastasis. This could, either maximize the current chemotherapeutic agents or greatly reduce, the lethal aspect of cancer. Future work will also examine the potential anti-tumor therapeutic strategy of using specific A2A-adenosine receptor antagonists for TME modulation. Of which, PBF-1129 is undergoing pre-clinical and IND-enabling studies and demonstrates high anti-tumor efficacy, suggesting the possibility for clinical trials with A2A- antagonists for cancer therapy in the nearest future. Lastly, our methodology is targeting a glaring hole in the understanding of tumor metastasis, meaning the forthcoming information from our work holds great promise to identify novel therapeutic strategies aimed at greatly diminishing the chief cause of cancer morbidity.

Keywords: Tumor immunology, Tumor microenvironment, adenosine signaling

P2.04-028 CONE-BEAM CT VIRTUAL NAVIGATION-GUIDED PERCUTANEOUS NEEDLE BIOPSY OF SUSPICIOUS PLEURAL METASTASIS: INITIAL EXPERIENCE

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Background: Among pleural lesions showing dense or nodular thickenings, malignancies, particularly metastases, have been shown to be more common than benign diseases. Since the diagnosis of pleural metastasis can prevent unnecessary surgical interventions in oncologic patients, the accurate diagnosis of pleural metastasis would be of great clinical importance. Pathologic diagnosis with solid tissue samples remains critical for this, particularly for cytology negative cases. Recently, cone-beam CT (CBCT) was introduced to the field of radiology as an advanced cone-beam CT has provided high diagnostic accuracy and efficacy of percutaneous transthoracic needle biopsy of lung nodules and mediastinal masses. In addition, the CBCT virtual navigation software program is able to provide a virtual needle pathway leading to better targeting of lesions, helping operators more easily navigate the needle into the target after initially determining the skin entry site and destination target based on pre-procedural CBCT data. Yet, CBCT virtual navigation has not been investigated for pleural biopsy. Therefore, we aimed to assess the usefulness of the CBCT virtual navigation system for percutaneous biopsy of pleural lesions with regard to its diagnostic accuracy and complication rates for clinically or radiologically suspected pleural metastasis.

Methods: This retrospective study was approved by our institutional review board with waiver of patients’ informed consent. From December 2010 to April 2016, 38 CBCT virtual navigation-guided pleural biopsies were performed in 36 patients (M:F=18:17, mean age, 64.61 years ± 12.67) with clinically or radiologically suspected pleural metastasis. A coaxial system with 18- or 19-gauge cutting needles was used. Procedural details, diagnostic

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Insidious symptoms often treated for benign obstructive airways diseases and respiratory infections, over a mean of 15 (range 3-31) months. About half had normal CXR as the tumor was distributed most frequently in the trachea (66.2% of 13) followed by the main bronchi (30.8%), lobari bronchi (23%). Six (66.2%) patients, all with adenoid cystic carcinoma, underwent emergent bronchoscopic intervention to secure greater airway patency before definitive therapy with surgery or/and radiotherapy. All airways interventions were performed via the rigid bronchoscope under deep intravenous sedation and/or endotracheal intubation. The types of interventions included: NOFAG (8), balloon dilatation (all 13), rigid tube or forceps resection (13), balloon dilatation (7) and silicone stenting (3). There were no procedural complications. Two patients, both with typical carcinoid, had bronchoscopic curative resection and the majority (9 out of 13) of the patients underwent surgery. External beam radiotherapy was administered to 5 (38.5%) of the patients when surgical resection was deemed not feasible (2) or with positive margins (3). None received systemic therapy. Prolonged good palliation was achieved for 4 (30.8%) patients with surgically unresectable lesions or recurrences via endoscopic therapy with or without radiation, including brachytherapy. The mean follow up duration was 64 (range 28-100) months. Conclusion: Airway intervention for low grade malignant bronchogenic neoplasm is an important part of the therapeutic armamentarium. Its role may be 1) emergent for critical airway obstruction where establishment of adequate airway patency is necessary prior to definitive therapy with surgery and/or radiotherapy, or 2) curative for those who present with a symptom (e.g., endobronchial, pleural, cutaneous). In this cohort, there are differences in the rate of surgical resection and the mode of therapy used. Although more than half of the patients underwent surgery, the rate of survival in patients who had surgical resection was 66.2% versus 53.8% in those treated with endobronchial therapy alone. Based on these results, we recommend endobronchial therapy as a first line approach for managing low grade malignant bronchogenic neoplasm as it is associated with a higher rate of survival. Further studies are needed to confirm these findings.

Keywords: Interventional bronchoscopy

P2.04-031 PREDICTORS OF PATHOLOGICAL COMPLETE RESPONSE (TRG=1) AMONG ESOPHAGEAL CANCER CASES; NCI POOLED DATA

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Background: Commonly used chemotherapy regimens for esophageal cancer(EC) are EOX(Epirubicin/Oxaloplatin/Capecitabine) for adenocarcinoma and CF(Cisplatin and 5-Flourouracil) for squamous carcinoma. In this study we aim to assess prevalence of pathological complete response(pCR) among current chemotherapeutic regimens among our EC cases and compare pCR cases to the remaining cohort Methods: We retrospectively reviewed Pathology Department database to retrieve EC patients treated in our National Cancer Institute(NCI), Cairo University during the past 5-years. Available variables were age, gender, operation, diagnosis, tumor size and grade, LN-size, presence of Barrett’s esophagus or in-situ/micro-invasive carcinoma, gross and microscopic pictures. MANDARD’s pathological response using tumor regression grade(TRA) was quantitated into five grades(1-5) with TRG=1 showing absence of residual cancer(Mandard et al, 1994).Esophageal carcinoma regression after chemoradiotherapy,Cancer,73(11),2680-86). Logistic regression was used to identify pCR(TRA=1)predictors. Kaplan-Meier survival curve results were used. Results: 334 patients were encountered with males predominance,206(61.5%), Median age was 64.4(inter-quartile range,IQR,58.58-68), Pathology was ScC in 227(68%), adenocarcinoma in 94(28.1%), and undifferentiated ca in 9(2.7%) and others in 4(1.2%). pCR(TRA=1) was evident in 15 cases(4.5%). Among mentioned variables, only advanced age, non ScC and high grade tumors adversely affect pathological response to induction treatment. On MVA, Advanced age (Odds Ratio(OR)=0.923,95%Confidence interval(CI)=0.86-0.99) p=0.025, moderate/ high grade tumors(OR=0.03,p=0.001) adversely affect response while ScC pathology has better response trend(OR=0.9, p=0.086). 3-years overall survival (OS) was 100% in pCR(TRA=1) vs 82.3% in the remaining cohort(Figure). Among esophagectomy cases, survival was 71.7%for males vs28.3% for females(p=0.093). Gastric pull up was performed in all surgical cases. RI was present in 2.2%. Median tumor size was 4.3cm(IQR, 3.5-5.6cm),least surgical margin was 3(2-4)and max(LN)size was 1(1-2)cm. Median +veLN, total LNNumber&LN-Ratio was(0.1,1.7) for 0.0% (95% CI). None of patients had prostatectomy cases, survival was 59.5% for 3-years OS among esophagectomy patients was 79.6%. Conclusion: Young EC patients and low grade tumor show better response to chemotherapy so aggressive treatment is warranted among this cohort. ScC carries a good prediction to pathological response and hence better survival mandating aggressive chemoradiotherapy in this cohort aiming to cure.

Keywords:
Keywords: Pathological complete response (pCR), Tumor regression grade (TRG), overall survival (OS), Esophageal cancer, chemotherapy

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Background: Salivary gland type neoplasms are known to occur at multiple organ sites in view of basic structural homology among exocrine glands in these anatomic sites. Primary salivary gland type tumors of lung (PSGTL) are rare intra-thoracic malignant neoplasm. They are believed to arise from the sub-mucosal glands of the trachea-bronchial tree. Their description in literature is largely limited to a few case series/case reports. A greater awareness of PSGTL is essential for accurate diagnosis and proper clinical management. A systematic review and pooled analysis of previously reported cases of PSGTL is presented here

Methods: We searched the electronic database of Pubmed using key words ("lung neoplasm"[Mesh] AND "salivary gland tumors"[Mesh]) to identify the papers documenting the PSGTL. Filters (publication date from 1900/01/01 to 2015/12/31, Humans, and English) were applied to refine the search. All the articles which were single case reports or had exclusively presented one pathological type of PSGTL were not included in the review. A pooled analysis of clinical, pathological, treatment-related and survival data was performed. Results: The present systematic review included 5 studies and a total of 233 patients. Mean age of the patients was 41 years (range 6-80 years) and there was a male preponderance (1.3:1). Common pathological types were mucoepidermoid (MEC) (56.6%), adenoid cystic (ACC) (39.5%), and epithelial-myoepithelial cancer (3.8%). Tumors were located in central airways (trachea and major bronchi) in 43.3% patients. Mean tumor size was 4.2 cm. Surgery was the primary treatment undertaken in 82.4% patients while radiotherapy and chemotherapy was also used in 15.9% and 9.4% patients. Lymph node involvement was seen in 15.2% patients. Disease recurrences were observed in 21.1% patients (12.9% and 37.5% in MEC and ACC respectively). 3-year, 5-year, and 10-year overall survival was 86.4%, 64.1%, and 73.6% (93.8%, 90.0% and 85.0% respectively for MEC), 76.7%, 62.8% and 50.5% respectively for ACC). Conclusion: Surgery is the primary treatment of PSGTL resulting in good long-term survival. ACC histological type has a poor prognosis with more disease recurrences compared to MEC. Role of chemotherapy and radiotherapy in the management of PSGTL warrants further studies.

Keywords: Salivary gland neoplasms, Mucoepidermoid cancer, Lung neoplasms, Adenoid cystic cancer

P2.04-032 PULMONARY SARCOMATOID CARCINOMA (PSC): EXPERIENCE OF 45 PATIENTS AT A COMPREHENSIVE CANCER CENTER

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Background: Pulmonary sarcomatoid carcinoma is rare and standard therapy is not well defined. We evaluated experience at our center to identify factors influencing the outcome. Methods: We performed a retrospective review of PSC patients (pts) treated at Roswell Park Cancer Institute between 1972 and 2014. Results: 45 pts were identified. Cohort consisted predominantly of males (55%), Caucasians (91%) and smokers (87%) with an average 47 pack-year smoking history. Median age at diagnosis was 63 years. 22% were presented with stage I, 25% with stage II, 22% with stage III and 31% with stage IV at diagnosis. All 13 pts tested for EGFR mutation were wild type. Mutations in KRAS were present in 3/11, ROS1 in 0/2, ALK in 0/9, RET in 0/2, BRAF in 0/2 and MET amplification in 1/2 pts. 29 pts underwent surgery. 80% had video assisted thoracoscopic surgery with 25 undergoing lobectomy and 3 pneumonectomy. 7 pts (16%) had neoadjuvant chemotherapy (CT), 6 of these received a cisplatin-based doublet (with gemcitabine, paclitaxel or pemetrexed), 1 received sarcoma-like regimen with cisplatin, paclitaxel and ifosfamide. 6 pts had partial response (PR) and 1 had progressive disease (PD). Adjuvant chemotherapy (AC) consisting of a platinum-based doublet was given in 10 pts. 41% pts who underwent surgery relapsed. Local relapse was the most common (77%). Systemic CT was given in 19 pts with stage IV or relapsed disease. First line CT was a platinum-based doublet in 74% pts. After a median of 2 cycles, only 1 patient had PR and 1 had stable disease. 88% pts had PD on first-line CT. Second-line CT was given in 11 pts, with combination or single agent (platinum, docetaxel, irinotecan, pemetrexed) or EGFR inhibitors in 3 pts. 5 pts underwent third-line CT. No pts had response to second- or third-line CT. Median progression free survival (PFS) was 4.9 months (m) and overall survival (OS) was 12.2 m and significantly depended on stage at diagnosis. Stage IV pts had PFS of 2.4 m and OS of 3.4 m. Pts receiving AC had significantly improved PFS (37 vs 13 m; p=0.026) and OS (48 vs 22 m; p=0.025). Conclusion: PSC heralds a poor prognosis and no standard management guidelines exist. AC is associated with significant improvement vs 22 m; p=0.025). Conclusion: PSC heralds a poor prognosis and no standard management guidelines exist. AC is associated with significant improvement in survival. Local relapse is the most common failure pattern in early-stage disease. In advanced stages, cytotoxic CT is ineffective with a short survival. There is a dire need for newer therapies.

Keywords: Sarcomatoid Carcinoma, pulmonary sarcomatoid cancer, poor prognosis, chemotherapy

P2.04-033 PRIMARY SALIVARY GLAND TUMORS OF THE LUNG: A SYSTEMATIC REVIEW AND POOLED ANALYSIS

Poster Session - P2.04: MESOTHELIOMA/THYMIC MALIGNANCIES/ESOPHAGEAL CANCER/OTHER THORACIC MALIGNANCIES – TUESDAY, DECEMBER 6, 2016

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Background: To assess the role of secreted protein, acidic and rich in cysteine (SPARC) and β-tubulin III (TUBB3) in predicting the clinical outcomes of Chinese ESCC patients receiving nab-paclitaxel plus docetaxel neoadjuvant chemotherapy. Methods: The clinical data and tumor biopsies prior treatment from 35 stage II-III ESCC patients receiving nab-paclitaxel plus cisplatin from July 2011 to December 2012 were retrospectively collected and analyzed for SPARC and TUBB3 expressions by immunohistochemistry. The relationships between expressions of SPARC/TUBB3 and response or survival were determined by statistical analysis. Results: All patients received two cycles neoadjuvant CT. 30/35 patients accepted surgery (85.7%). 24/30 patients (80.0%) received adjacent CT, and 7 patients (23.3%) among them received adjacent radiotherapy. 30 had R0 resection (100%). Pathological complete response (pCR) was achieved in 4 patients (13.3%). Near pCR (microfoci of tumor cells on the primary tumor without lymph nodal metastases) was acquired in 2 patients (6.7%). Down-staging was observed in 19 of 30 patients (63.3%). SPARC and TUBB3 statuses were evaluated in 22 patients. There was no significant correlation between TUBB3/SPARC status and clinical response. The median PFS in TUBB3 negative staining samples was longer than those in TUBB3 positive staining samples, although there was no statistical difference of OS between two groups. The median PFS/OS in SPARC negative staining samples and SPARC positive staining samples have no statistical difference. Conclusion: Not applicable

Poster Session - P2.04: MESOTHELIOMA/THYMIC MALIGNANCIES/ESOPHAGEAL CANCER/OTHER THORACIC MALIGNANCIES – TUESDAY, DECEMBER 6, 2016
P2.04-035 SURGICAL PERPLEXITIES IN A RARE CASE OF SYMPTOMATIC MEDIASTINAL LYMPHANGIOMA
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Background: Mediastinal lymphangiomas are very rare and are often found in close proximity to vital structures of the head and neck. Thus, the surgical approach can be challenging. It is debatable to employ open surgery techniques via a trap-door incision or median sternotomy in attempt to achieve complete surgical resection for a benign lesion. We report a case of symptomatic mediastinal lymphangiomia that was successfully managed with a Video Assisted Thoracoscopic Surgery (VATS) approach.

Methods: A 70-year-old male presented with no significant past medical history found in close proximity to vital structures of the head and neck. The patient made an uneventful recovery and was discharged home on the first post-operative day. Histological examination showed lymphoid aggregates and dilated lymphatic spaces with a rim of smooth muscle that are typical of lymphangiomas. She remained well and pain free at her 1yr follow-up clinic.

Conclusion: In conclusion, due to the unique nature and characteristics of mediastinal lymphangiomas, pre-operative diagnosis and treatment are challenging. Minimally invasive techniques for maximum debulking are useful for symptomatic treatment as complete resection may not always be possible.

Keywords: video assisted thoracoscopic surgery, lymphangiomia

P2.04-036 GIANT PRIMARY DEDIFFERENTIATED LIPOSARCOMA OF THE ANTERIOR MEDIASTINUM: AN EXTREMELY RARE OCCURRENCE
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Background: To present an extremely rare case of primary dedifferentiated liposarcoma of the anterior mediastinum. Methods: A 70-year-old male presented for persistent dyspnoea. Chest CT-scan showed a huge well-defined solid mass with a fatty tissue component in the left superior mediastinum, extending to the supraclavicular region, measuring approximately 4.6 x 4.9 x 7.4 cm, encasing the left carotid, subclavian and vertebral arteries, and the left internal jugular and brachiocephalic veins. Ultrasound guided core biopsy was inconclusive.

Results: The patient underwent surgery via left VATS approach. Frozen section of the lesion revealed partial lymphoid infiltration and scattered cystic-like spaces. No atypical cells or malignancy was seen. Minimal debulking of the lesion was performed with the aid of bipolar diathermy and harmonic ultrasonic energy devices instead of a complete resection. The patient was discharged on the 5th post-operative day.

Conclusion: Primary dedifferentiated liposarcoma of the mediastinum is extremely rare. Chemotherapy and radiotherapy seems to be ineffective; radical surgical resection represents the best therapeutic modality. A closed and long-term follow-up is required because of the high risk of recurrence.

Keywords: mediastinum, liposarcoma

P2.04-037 SOLITARY FIBROUS TUMOR OF THE PLEURA ASSOCIATED WITH SEVERE HYPOGLYCEMIA: THE DOEGE-POTTER SYNDROME
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Background: To present an extremely rare case of Doege-Potter Syndrome (DPS). Methods: A 66 years-old man, non-smoker, was admitted for disorientation and confusional state. Blood tests showed a severe hypoglycemia (30 mg/dl); the patient was not diabetic and did not take antihyperglycemic agents. An extremely low values of insulin and C-peptide was also found. A chest CT-scan showed a 20x16cm lobulated mass occupying the right hemithorax (Figure 1A). FDG-PET showed a unique uptake of the lesion (SUVmax 2.5). After a multidisciplinary discussion, a surgical resection was proposed. The lesion of pleural origin was radically resected through a right posterolateral thoracotomy. From the 1st postoperative day, the blood glucose levels were normal; the patient was discharged on the 5th postoperative day uneventfully. Results: The mass measured 26x18x12cm, presented polylobated margins, elastic consistency and grayish-white color (Figure 1B). Microscopically, a mesenchymal neoplasm characterized by spindle cells with moderate atypia, hyperchromasia and nuclear pleomorphism, organized in a fascicular pattern was found (Figure 1C). A moderate deposition of collagen extracellular matrix, with areas of hyaline involution and foci of necrosis was evident (Figure 1D). The mitotic index was 9/20HPF. Immunohistochemically, tumour cells were positive for CD94, CD99, BCL2, vimentin, desmin, IGF1-R, IGF-2, Ki67 (15%) and negative for EMA, smooth muscle actin, cytokeratin pool, c-kit, DOG-1, myogenin, calretinin, S100. Considering these histopathologic features, a diagnosis of malignant solitary fibrous tumor of the pleura was made. After 18 months, the patient is in good condition and free of disease.

Keywords: mesenchymal tumor, neoplasia, pleura
P2.04-039 LONG-TERM RISK OF RECURRENCE IN BENIGN PLEURAL TUMOURS

Background: Solitary fibrous tumor (SFT) is a rare tumor of submesothelial origin that can occur in the abdomen, extremities, trunk, head, neck and pleura. Pleural SFTs are defined as benign or malignant based on the number of mitoses and the presence of pleomorphism, hemorrhage, or necrosis. There is limited data in the literature regarding the recurrence risk of benign pleural SFT and the need for long-term follow-up in these patients. Methods: A single institution retrospective chart review was performed on all surgically resected primary pleural SFTs between 1992 and 2015. Preoperative clinical information, pathologic tumor characteristics, and long-term recurrence and survival data were collected. Results: There were 29 primary pleural SFTs resected between 1992 and 2015. Patients had a mean age of 60 years and there were 16 men (55%) and 13 women (45%). Fourteen (48%) presented with symptoms, including two patients with paraneoplastic syndromes, and the other 15 tumors (52%) were found incidentally on imaging. There were six giant SFTs defined as size greater than 15 cm, with two of six giant SFTs undergoing preoperative embolization to aid surgical resection. Otherwise, there was no neoadjuvant or adjuvant treatments in any patient. There was no perioperative 30-day mortality (0%). Mean follow up time was 77 months, during which 4 (14%) patients resected and 21 of 29 patients (72%) were alive at last follow up. Three of the 8 deaths occurred in patients with recurrent disease. Among the 19 benign pleural SFTs, 2 (11%) recurred at 5 and 9 years postoperatively and 2 of the 6 malignant SFTs (33%) recurred at 4 and 15 years postoperatively. Margin status was known in 25 cases, of which 21 (84%) were negative and 4 (16%) were positive. There were no recurrences in patients with known negative margins. Conclusion: This study represents one of the largest contemporary single institution reviews of outcomes of pleural SFT. While benign pleural SFTs were less likely to recur than malignant pleural SFTs, benign pleural SFTs with positive or unknown margin status remain at risk for recurrence up to a decade following resection and require ongoing long-term follow up and surveillance imaging.

Keywords: Pleural solitary fibrous tumor, Hemangiopericytoma

POSTER SESSION 2 – P2.04: MESOTHELIOMA/THYMIC MALIGNANCIES/ESOPHAGEAL CANCER/OTHER THORACIC MALIGNANCIES – TUESDAY, DECEMBER 6, 2016

P2.04-040 PLEURAL EFFUSION CHARACTERISTICS AND OUTCOMES IN CANCER PATIENTS

Background: Pleural effusion is a common occurrence in cancer patients, with an estimated annual incidence of 150,000 in the United States. It generally represents advanced malignant disease with median survival of 3 months. It can lead to debilitating symptoms such as dyspnea and pain, adversely affecting the quality of life. Methods: We performed a retrospective analysis of a dataset of 62 cancer patients with pleural effusion after first thoracentesis procedure. The recorded data included: age, gender, type of cancer, number of thoracentesis, pleural fluid volume characteristics and volume. Results: We studied 62 patients, with ages between 20-77 years, median 57 years; 64% were females and 36% were males. The number of patients deceased by the end of follow up was 43 (68.4%), alive at the end of follow up was 8 (12.9%), lost to follow up 11 (17.7%). Median overall survival was 3 months. The cancer type was divided into breast, 32.3%, non-small cell lung, 25.8% and 41.9% other cancers. Thirty-three (53.2%) patients had malignant pleural effusion with a median of 3 months of survival. Twenty-nine (46.8%) patients had non-malignant effusion with a similar median survival of 3 months. We analyzed the correlation of the radiologically estimated effusion volume, thoracentesis volume and presence of blood and malignant cells with outcomes (overall survival, OS). There is a negative correlation between the radiologically estimated effusion volume and OS (Pearson rank correlation of -0.43). This negative correlation is maintained in subgroup analysis (breast -0.56; lung -0.33). The thoracentesis volume was also negatively correlated with OS (Pearson rank correlation of -0.45), finding also maintained in subgroup analysis (breast -0.39, lung -0.66). We found no statistically significant difference in OS between malignant effusions (average OS 6.5 months, median 3 months) and non-malignant effusions (average OS 6.9 months, median 3 months). There was no statistically significant difference in survival between bloody effusions (average survival

Keywords: SOLITARY FIBROUS TUMOR OF THE PLEURA, hypoglycemia

POSTER SESSION 2 – P2.04: MESOTHELIOMA/THYMIC MALIGNANCIES/ESOPHAGEAL CANCER/OTHER THORACIC MALIGNANCIES/ESOPHAGEAL CANCER AND OTHER MALIGNANCIES – TUESDAY, DECEMBER 6, 2016

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3.5 months, median survival 1.25 months) and non-bloody effusions (average survival 6.2 months, median 3.5 months). Conclusion: We found an inverse correlation between the radiologically estimated pleural fluid volumes and OS as well as between thoracentesis volume and OS among cancer patients. This correlation is maintained in subset analysis of the two most common types of cancer in our sample, breast and NSCLC. Survival was not influenced by the presence of malignant cells or blood in the pleural fluid. A prospective study to better characterize the prognostic value of first thoracentesis may be warranted.

Keywords: metastatic cancer, pleural fluid

P2.04-041 TWO CASES OF PULMONARY SCHWANNOMA
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Background: Schwannomas are benign tumors that arise from peripheral, spinal, or cranial nerves. They occur commonly in the head, neck, and flexor surfaces of upper and lower extremities, but rarely in the bronchi or the lungs. Methods: We encountered two cases of pulmonary schwannoma treated with surgical resection, and reviewed previous reports on the clinical and pathological features of this disease. Results: Case 1: A 69-year-old woman was admitted to a regional hospital with symptoms of cough and appetite loss. Computed tomography (CT) revealed a tumor in her left lung, and obstructive pneumonitis in the left lower lobe. After undergoing treatment for pneumonitis with antibiotics, she was transferred to our hospital for further examination of the tumor. Bronchofiberscopy revealed a polypoid mass with a smooth surface, which near completely occluded the left lower lobe bronchus. Transbronchial biopsy did not provide a definite diagnosis. 18-Fluoro-deoxyglucose (FDG) positron emission tomography (PET) detected mild FDG uptake in the tumor (maximum standardized uptake value: 3.2). Because of the arriving clinical suspicion of malignancy in this tumor, the patient underwent surgical treatment. We initially considered left lower lobectomy or left lower sleeve lobectomy as curative surgical procedures, but eventually we performed left pneumonectomy because the tumor was tightly adhered to the upper pulmonary vein. Histopathological examination revealed that the tumor was composed of spindle cells arranged in a fascicular pattern without abnormal mitosis. Immunohistochemical staining demonstrated positive staining in the tumor cells for S-100 protein. On the basis of these findings, the tumor was diagnosed as a bronchial schwannoma. Case 2: A 54-year-old man was referred to our department, because he had an incidentally detected an abnormal shadow in the right lung field. Chest CT examination revealed the presence of a 7 mm, well-defined nodule in the periphery of the right middle lobe. 18-FDG PET did not show significant FDG uptake within the nodule. We could not exclude the possibility of malignancy; therefore, we performed video-assisted thoracoscopic wedge resection of the right middle lobe for diagnosis, as well as treatment. Intraoperative frozen sections suggested that the tumor was a hamartoma or a spindle cell tumor. Postoperatively, the permanent section was examined, and the diagnosis of pulmonary schwannoma was confirmed. Conclusion: We present two cases of pulmonary schwannoma, which is an extremely rare disease. In both cases, we did not obtain a definite diagnosis before surgery. Surgical treatment should be considered when malignancy cannot be excluded.

Keywords: Surgical resection, pulmonary schwannoma

P2.04-042 EPITHELIAL-MYOEPITHELIAL TUMOUR OF UNKNOWN ORIGIN: AN INTERESTING CASE REPORT WITH UNEXPECTED OUTCOME
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Background: Tracheobronchial submucous glands can be considered the pulmonary equivalent of minor salivary glands and therefore develop most of the tumours originated in these. Nevertheless, in spite of the wide distribution of this kind of glands along the tracheobronchial tree, pulmonary salivary gland-like neoplasms are not very frequent. Among them, most frequent are mucoepidermoid and adeno cystic carcinomas. On the contrary, pulmonary neoplasms showing a mixture of epithelial and myoepithelial elements are extraordinary infrequent, with only 20 cases in literature. Methods: We present the case of a 55-year-old man complaining for bone pain and mobility deterioration. Results: The patient was hospitalized to exclude all possible reasons of malignant bone infiltration. His X-ray scanning showed multiple lytic infiltration of unknown malignant origin. A PET/CT scan performed did not reveal any area implying the primary malignancy development. Bone biopsy taken post macro and microscopic study, diagnosis of epithelial-myoepithelial tumour was hinted. Our case has the peculiarity of being connected neither to breast nor to salivary glands as expected, a characteristic not reported in any literature reviewed case. These tumours have been named in a lot of different ways, including adenomyoepithelioma, epithelial-myoepithelial tumour, epithelial-myoepithelial carcinoma or epithelial-myoepithelial tumour of uncertain malignant potential. The p27kip-1 protein plays a fundamental role in the development of these neoplasms. The suggested therapeutic agents are platinum/taxane combinations with no excellent prognosis as an unknown outcome. The palliative care is often proposed due to the deteriorated performance status. Our patient underwent combined radiotherapy and bisphosphonate infusion with pain relief and mobility improvement. The patient, 2 years later, is still alive, under bisphosphonate support and no primary malignant has identified. Conclusion: It is not rare to have prolonged outcome and satisfactory improvement in Epithelial-myoepithelial tumour even in primary malignant lesion identification. Individualized therapeutic approach is always proposed

Keywords: glands, myo epithelial tumour, lytic lesions, unknown malignant origin

P2.04-043 SQUAMOUS CELL CARCINOMA ARISING FROM THE PLEURA. AN INTERESTING CASE REPORT
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Background: Squamous pleura carcinoma is a very rare entity with sporadic literature reports. Literature research reveals 12 reports of squamous carcinoma arising from pleura in patients with chronically draining empyema or locally deteriorated inflammation. Methods: We state an unusual interesting case report of primary squamous pleura carcinoma and present relevant literature surveillance. Results: The patient, 68 years old, male, heavy smoker, reported constant right chest pain and experienced dyspnea recently started. His chest X ray revealed pleural effusion and mesothelioma infiltration was suspected. Endoscopy revealed no abnormalities. Subsequent CT scan showed 4cm mass arising from pleura and a computed tomography scan revealed an expanded mass in the right thoracic cavity, involving the surrounding tissue. He underwent needle biopsy ultrasound guided. The macroscopic pathologic findings demonstrated a greyish-white mass with hemorrhage beneath the pleura. They revealed multifocal, poorly-differentiated, squamous cell carcinoma with histology that was distinctly different from that of original lung cancer arise and consistent with pleura (p63+, CK5/6+, p40+, TTF-1+). He received 1rst line chemotherapy treatment with platinum based combination with taxane and the patient had an excellent response with no effusion production and rapid thoracic pain and dyspnea relief. He is still in excellent status post 6 cycles chemotherapy, with no evidence of disease deterioration. The final scope of surgical total resection is being considered. Conclusion: Cases of squamous cell carcinoma arising from pleura in patients with a chronically draining empyema or inflammation cavity are rare. The documented in literature review chemotherapy combinations are of limited expectations and no complete response is reported when rare reports are documented. We suggest a thorough pathologic study when pleura masses are found to exclude the common mesothelioma diagnoses since seldom entities as pleura cancers need an individualized therapeutic manipulation.

Keywords: pleura, thoracic mass, effusion, squamous cell

P2.04-044 MEDIASTINAL NEUROGENIC TUMORS

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POSTER SESSION 2 – P2.04: MESOTHELIOMA/THYMIC MALIGNANCIES/ESOPHAGEAL CANCER/OTHER THORACIC MALIGNANCIES

ESOPHAGEAL CANCER AND OTHER MALIGNANCIES – TUESDAY, DECEMBER 6, 2016

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POSTER SESSION 2 – P2.04: MESOTHELIOMA/THYMIC MALIGNANCIES/ESOPHAGEAL CANCER/OTHER THORACIC MALIGNANCIES

ESOPHAGEAL CANCER AND OTHER MALIGNANCIES – TUESDAY, DECEMBER 6, 2016
Abstracts

HISTOPATHOLOGICAL CHARACTERISTICS AND SURGICAL TREATMENT IN A SINGLE-INSTITUTIONAL EXPERIENCE
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Background: Intrathoracic neurogenic tumors are uncommon and typically originate from the peripheral nerves, paraganglionic nerves, or the autonomic nervous system. They are commonly found in the mediastinum, especially in the posterior mediastinum and have a variety of clinical and histological features. Mediastinal neurogenic tumors in adults are generally benign, but may be malignant. Methods: We retrospectively reviewed our institutional experience of mediastinal neurogenic tumors from 2010 to 2015. The patients were evaluated according to age, gender and histological characteristics of the tumor. Results: There were 78% males and 22% females diagnosed with mediastinal neurogenic tumors. Mean age was 46.8±12 years. Distribution according to the histopathological diagnosis was: 56% schwannoma, 22% malignant schwannoma, 22% ganglioneuroma. The operative procedure performed in all cases was tumor extirpation through thoracotomy. In 10% of cases, presence of intraspinal growth was encountered (the so-called “dumbbell tumors”), thus hemilaminectomy was performed. There were no operative deaths and minimal morbidity. Mean postoperative stay was 5 days. Conclusion: In this study, the most common mediastinal neurogenic tumor found was schwannoma. Neurogenic tumors arising in the mediastinum are generally of benign nature and mostly found in males. The treatment choice for malignant and benign mediastinal neurogenic tumors is complete resection for the purposes of avoiding local invasion, facilitating differential histopathological diagnosis and preventing malignant degeneration. The surgical management of the dumbbell tumors differs from others.

Keywords: mediastinum, Neurogenic tumors

P.02.04-056 MANAGEMENT OF MALIGNANT PLEURAL EFFUSIONS: TEN YEARS EXPERIENCE OF A SINGLE CENTER
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Background: Malignant pleural effusions (MPE) are a common clinical problem for patients with neoplastic disease. MPE may be an accompanying sign of metastatic disease and may also develop due to direct invasion. MPE may be due to a variety of causes. Methods: We present our institutional experience for management of malignant pleural effusions for a period of ten years where have been examined all clinical cartels of patients with pleural effusions. All data are analyzed with Pearson Chi-square test. Results: This study has demonstrated that MPE represent 10% of all pleural effusions. 46% of them have been smokers. 53% of MPE was in the right hemithorax, 38% in the left hemithorax and only 9% was bilateral. The age range was (18-91), and the average age was 63 years old. 37% of these patients have had recent surgery for neoplasia, and in 27% there is no information for recent malignancy and pleural fluid was the first sign of patients. 14% of these patients have relatives with neoplasia. 48% of the cases underwent to biopsy via Video Assisted Thoracic Surgery (VATS). In 83% of cases definitive surgical treatment was pleural drainage and chemical pleurodesis. Up to (60% of cases). Most patient are asymptomatic (50%) although dyspnea, cough, chest pain, hemoptysis can occur. By immunohistochemistry, MPE shows the typical markers of vascular differentiation. Primary epithelioid hemangioendotheliomas of pleura are extremely rare, usually affecting males, and associated with a variety of clinical manifestations and poor prognosis. We present a rare case of MPE with pleural effusion involvement. Results: A 50-year-old non-smoking woman presented to our institution complaining of persistent cough and progressive dyspnea. This was first treated with antibiotics without improvement of the symptoms. Chest computed tomography (CT) showed multiple disseminated nodules of both lungs mostly involving the upper lobes with associated right-sided pleural effusion and thickening. There is a elevated serum level of Cancer Antigen (CA) 125. In a right triportal video-assisted thoracoscopic surgery (VATS) we performed wedge resections of the right upper, middle and lower lobes with diffuse nodular process and multiple biopsies of thickened pleura. Results: Pathological examination of the pleuro-pulmonary samples showed multiple, diffuse nodular infiltrates of epithelioid cells with frequent cytoplasmic vacuoles, rare mitoses and foci of tumor necrosis. Immunohistochemistry was positive for Vimentin, CD31, CD34, ETS-related gene (ERG). Therefore, a final diagnosis of Epithelioid hemangioendothelioma was made on the basis of the radiographic, cytological, and immunohistochemical findings. Conclusion: Pulmonary Epithelioid hemangioendothelioma is a vascular tumor with low to intermediate-grade malignancy. Pleural epithelioid hemangioendothelioma is less common and the clinical behavior is more aggressive and has a poorer prognosis. Our case is an epithelioid hemangioendothelioma with a clinical and pathologic pleuro-pulmonary involvement and a very aggressive clinical course.

Keywords: rare vascular neoplasms, endothelial markers, epithelioid hemangioendothelioma, pleuro-pulmonary tumor

P.04-046 A RARE CASE OF PLEURO-PULMONARY EPITHELIOD HEMANGIOENDOTHELIOMA
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Background: Epithelioid hemangioendothelioma (EHE) of lung and pleura are rare vascular neoplasm with an epithelioid and histiocytoid appearance that originated from tissue endothelial cells. Pulmonary EHE was first described as “intravascular bronchioalveolar tumor” (IVBAT) by Dail et al. in 1975, since it was believed to be an aggressive form of bronchoalveolar cell carcinoma with propensity to invade adjacent blood vessels. It is described by the World Health Organization 2012 classification as lesion locally aggressive with metastatic potential, a neoplasm of low to intermediate-grade malignancy. It occurs with a predilection for younger (mean age 39) female (60% of cases). Most patient are asymptomatic (50%) although dyspnea, cough, chest pain, hemoptysis can occur. By immunohistochemistry, EHE shows the typical markers of vascular differentiation. Primary epithelioid hemangioendotheliomas of pleura are extremely rare, usually affecting males, and associated with a variety of clinical manifestations and poor prognosis. We present a rare case of EHE with a extensive pleuro-pulmonary involvement. Methods: A 50-year-old non-smoking woman presented to our institution complaining of persistent cough and progressive dyspnea. This was first treated with antibiotics without improvement of the symptoms. Chest computed tomography (CT) showed multiple disseminated nodules of both lungs mostly involving the upper lobes with associated right-sided pleural effusion and thickening. There is a elevated serum level of Cancer Antigen (CA) 125. In a right triportal video-assisted thoracoscopic surgery (VATS) we performed wedge resections of the right upper, middle and lower lobes with diffuse nodular process and multiple biopsies of thickened pleura. Results: Pathological examination of the pleuro-pulmonary samples showed multiple, diffuse nodular infiltrates of epithelioid cells with frequent cytoplasmic vacuoles, rare mitoses and foci of tumor necrosis. Immunohistochemistry was positive for Vimentin, CD31, CD34, ETS-related gene (ERG). Therefore, a final diagnosis of Epithelioid hemangioendothelioma was made on the basis of the radiographic, cytological, and immunohistochemical findings. Conclusion: Pulmonary Epithelioid hemangioendothelioma is a vascular tumor with low to intermediate-grade malignancy. Pleural epithelioid hemangioendothelioma is less common and the clinical behavior is more aggressive and has a poorer prognosis. Our case is an epithelioid hemangioendothelioma with a clinical and pathologic pleuro-pulmonary involvement and a very aggressive clinical course.

Keywords: rare vascular neoplasms, endothelial markers, epithelioid hemangioendothelioma, pleuro-pulmonary tumor

P.04-047 A RARE CASE OF EXTRAMEDULLARY PLASMACYTOMA OCCURRING IN THE POSTERIOR MEDIASTINUM
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Ospedali Riuniti Di Foggia, Foggia/Italy

Background: Extramedullary plasmacytoma (EMP) is a rare neoplasm that is derived from a monocolonal proliferation of plasma cells in the soft tissues or organs outside the bone marrow and is present in about 3% of all plasma cell neoplasms. The average age of patients is about 60 years. The most frequent site is the upper respiratory tract (approximately 80%). The endoractic forms usually manifest as nodules or pulmonary masses. Rarely may it present with mediastinal mass as a primitive solitary lesion. We present a case of extramedullary plasmacytoma of the posterior mediastinum. Methods: A 22 years old female presented to us with a history of chest pain, persistent cough, dysphagia, asthenia and dyspnea for few weeks. She denied smoking and had ischemic heart disease and atrial fibillation as comorbidities. Her serum protein electrophoresis and hemocytometric parameters were normal. Chest X-ray showed a posterior voluminous endotracheal opacity and chest Computed Tomography showed an expansive hypodense lesion of the posterior mediastinum of 15.6 x 9.1 cm, which surround and displaced the thoracic aorta causing compression of the esophagus and central airways without pathological lesions of the lung parenchyma and the presence of a modest bilateral pleural effusions. Tranbronchial needle aspiration under eco-endoscopic guide (EBUS-TBNA) has revealed the presence of isolated plasma cell neoplasm.

Keywords: rare case, extramedullary plasmacytoma, plasmacytoma
Abstracts


Background: Tracheal carcinoma of low grade malignancy is rare and experience of respiratory doctors on this tumor is limited. Therefore, the diagnostic and therapeutic experiences of doctors need to be discussed at major conferences. Methods: In this study, we encountered 3 cases of tracheal carcinoma, two were adenoid cystic carcinoma and one was mucoepidermoid carcinoma. All patients visited the hospital because of severe dyspnea. Results: Case 1. A 40-year-old woman had tracheal adenoid cystic carcinoma at the level of the sternal notch. After intubation using 5-mm tracheal tube, resection of five tracheal rings and reconstruction were completed through a cervical approach. She survived for 12 years postoperatively without recurrence. Case 2. A 44-year-old man with adenoid cystic carcinoma at the mid-trachea underwent resection of eight tracheal rings and reconstruction through mid-sternotomy. He survived for 14 years postoperatively without recurrence. Case 3. A 79-year-old woman who had cerebral hemangioma at the posterior mediastinal manifestations of EMP, it should be differentiated especially like a mediastinal mass as a primitive solitary lesion. In terms of posterior mediastinal manifestations of EMP, it should be differentiated especially like a mediastinal mass as a primitive solitary lesion. In terms of diagnosis of extramedullary plasmacytoma, the prognosis is very poor and worse than primitive forms. Therefore, precise and timely framing (classification) of the disease is essential for diagnostic and therapeutic purposes.

Keywords: multiple myeloma, plasma cell marker, extramedullary plasmacytoma, posterior mediastinum neoplasm


Background: Giant tumor almost occupied the entire one-side thoracic cavity could be surgically resected at the 8th day postoperatively. No adjuvant treatment was used. Follow-up shows no recurrence and metastasis. The
Background: Although it is known that chromium is an important inhaled carcinogen for lung cancer, there are few reports about genetic effects of chromium in oncogenic process. Our previous studies revealed that chromium exposure frequently had microsatellite instability (MSI), and that MSI was associated with the loss of expression of MLH1, which is one of the essential DNA mismatch repair proteins. Inactivation of MLH1 due to promoter methylation causes high level of microsatellite instability in hereditary nonpolyposis colorectal cancer (HNPCC). Therefore, we hypothesized that loss of expression of MLH1 in chromate lung cancer is caused by MLH1 promoter methylation similar to HNPCC. In the present study, we analyze DNA methylation of MLH1 promoter regions in chromate and non-chromate lung cancers and clarify whether methylation of MLH1 has the influence on MLH1 protein expression and MSI. Methods: Thirty-three tumor samples from chromate workers with lung cancer and thirteen tumor samples from non-chromate lung cancer were investigated in our previous studies. Results: High methylation levels of MLH1 promoter regions were found in 42.4% (7/33) of chromate lung cancers and 15.4% (2/13) of non-chromate lung cancers. Methylation rates of MLH1 promoter region and the grade of MSI were related to positive correlation in chromate lung cancers. Immunohistochemistry for MLH1 was performed in 24 chromate lung cancer, High methylation of MLH1 was found in 27.3% (6/21) of tumors with MSI within 3% (1/33) of samples without MSI. We concluded that MSI was correlated strongly with grade of MSI and expression of MLH1 in chromate lung cancer. Conclusion: According to the present data, DNA methylation of MLH1 promoter regions might contribute to loss of expression of MLH1 protein and MSI. We speculate that in addition to genetic changes, epigenetic events have emerged in chromium carcinogenesis.

Keywords: microsatellite instability, MLH1, promoter methylation, chromium

P2.04-053 SURGERY OF MULTIPLE LUNG METASTASES IN PATIENTS WITH SARCOMAS AND EPITHELIAL TUMORS
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Background: Pulmonary metastases are the most common recurrences of bone or soft tissue sarcomas and epithelial tumors. A role of surgical treatment in management of multiple lung metastases has not been well-established. We aimed to assess the rates of early post-operational complications and survival outcomes after pulmonary resection for multiple metastases. Methods: A series of patients who underwent pulmonary resections for multiple metastases (≥4) between January 2004 and December 2015 in Medical Radiological Research Center (Obninsk, Russia) were retrospectively evaluated. Perioperative clinical and histopathological data and long-time survival were analyzed. Results: Forty seven patients who received surgical treatment for multiple lung metastases have been included in the analysis (24 males). Mean age was 64 years (range 18-70). Twenty nine patients had primary diagnosis of bone or soft tissue sarcoma and 18 patients had epithelial tumors. All subjects received radical surgical treatment of primary cancer in combination with radiation therapy (in 25 subjects) or chemotherapy (in 35 subjects). The mean time to detection of lung metastasis was 15 months. Bilateral lung involvement was identified in 32 patients. Eighty four operations were performed (76 atypical resections, 6 lobectomy, 1 segmentectomy and 1 pneumonectomy). In average, 6 lesions were removed (range 4-103). Nd:YAG laser (length of wave 1318nm) used in 44 operations and electrocautery in 32 cases. In case of bilateral lesions surgical interventions were performed 4-6 weeks apart. In 4 patients metastatic process was not confirmed (tuberculosis, fibrosis and necrosis). Early postoperative complications were observed in 7 subjects (5 cases of pneumothorax, durable lymphorrhoea and plebothrombosis. The rate of postoperative complications were similar when laser (3/44) or electrocautery (4/32) were used. There was no mortality within 30 days post operation. Mean survival
time was 22.5 months (range 3.1-49 months). The duration of survival depends on histological type of primary tumor (21 months for patients with bone or soft tissue sarcoma and 46 months for patients with epithelial tumors). The survival time appeared to be shorter for patients with bilateral process than unilateral but the difference was not statistically significant (23.4 and 48 months, respectively, p=0.25). Conclusion: The development of distant metastases is associated with extremely poor survival of patients with sarcomas and epithelial tumors. Based on our observation we suggest that some patients with isolated lung metastases can benefit from aggressive surgical treatment. The controlled, prospective, large-scale clinical studies are required to further assess impact of surgical treatment on survival of these patients.

Keywords: laser, lung metastases, Surgery

Poster Session 2 – P2.05: Radiotherapy

Poster Session 2 – P2.04: Mesothelioma/Thymic Malignancies/Esophageal Cancer/Other Thoracic Malignancies

P2.04-054 Pleural CEA and C-Reactive Protein in Patients with Lung Metastases and Malignant Pleural Effusion. A Prospective Case-Control Study

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Background: Malignant pleural effusion (PE) is common cancer patients, and may require invasive investigations. The aim of this study was to evaluate the diagnostic utility of pleural carcinoembryonic antigen (pCEA) and pleural C-reactive protein (pCRP) assay in cancer patients with PE. Methods: We prospectively measured both pCEA and pCRP in 47 consecutive patients with a history of cancer and PE (cases). Controls were 41 age- and sex-matched patients with confirmed benign PE. There were 52 (63.4%) men and 39 (47.6%) women, with an overall median age of 71 years (range 40-88 years). Results: The age (p=0.943) and male-to-female ratio (p=0.254) did not differ significantly between groups. pCEA (54.9±10.8 mg/L vs. 1.5±1.3 mg/L; p=0.0001) was higher in patients with malignant PE, while pCRP was higher (11.7±7.2 vs. 5.5±3.4 mg/L; p=0.0001) in controls. The results are reported in the Table (95% CI).

The relative linear regression equation (Figure) was pCRP=11.725−0.573 pCEA, suggesting that the two markers were independent parameters.

RESULTS

<table>
<thead>
<tr>
<th></th>
<th>pCEA (mg/L)</th>
<th>pCRP (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cut-off</td>
<td>16 mg/L</td>
<td>5 mg/L</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>87.8% (77.8-97.8)</td>
<td>36.6% (28.5-51.3)</td>
</tr>
<tr>
<td>Specificity</td>
<td>67.2% (61.7-77.5)</td>
<td>67.6% (62.8-91.9)</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>52.2% (44.1-64.8)</td>
<td>57.7% (48.3-69.5)</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>66.7% (51.5-92.9)</td>
<td>60.6% (50.8-72.4)</td>
</tr>
<tr>
<td>Likelihood ratio positive</td>
<td>1.29</td>
<td>1.50</td>
</tr>
<tr>
<td>Likelihood ratio negative</td>
<td>0.38</td>
<td>0.65</td>
</tr>
<tr>
<td>False positive rate [a]</td>
<td>68.3%</td>
<td>2.4%</td>
</tr>
<tr>
<td>False negative rate [b]</td>
<td>12.2%</td>
<td>1.4%</td>
</tr>
<tr>
<td>Accuracy</td>
<td>47.6%</td>
<td>67.1%</td>
</tr>
</tbody>
</table>

Conclusion: The measurement of pCRP+pCEA together represents an accurate and easy to perform tool useful in differentiating between benign and malignant PE, and should be suggested in all cancer patients requiring PE analysis.

Keywords: C-reactive protein, malignant pleural effusion, lung metastases, Pleural CEA

Poster Session 2 – P2.05: Radiotherapy

P2.05-001 A7-NACR agonist GTS-21 reduces radiation-induced lung injury by inhibiting HMGB1/TLR-4/NF-κB pathway

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Background: The cholinergic anti-inflammatory signaling pathway allows the autonomic nervous system to modulate immunologic stimuli and inflammatory processes. α7 nicotinic acetylcholine receptor (α7-NACR) is a major component in this pathway. GTS-21, a selective α7 nicotinic acetylcholine receptor agonist, has been demonstrated as a promising treatment for inflammation. So, the aim of this study is to determine whether treatment GTS-21 can mitigate the radiation induced lung injury. Methods: C57BL/6 mice were randomly divided into three groups: a control group, a 12 Gy thoracic irradiation group, a 12 Gy thoracic irradiation group treated with 4mg/kg GTS-21 immediately after irradiation. Each of group were sacrificed at 1, 3, 7, 14, 21d and 3, 6m post-irradiation, and the sections were respectively stained with hematoxylin and eosin (H&E). Then, we analyzed the results to assess the degree of inflammation and fibrosis. Serum concentrations of TNF-α, IL-1β and IL-6 were quantitatively measured by Cytometric Bead Array (CBA) kit. Real-time PCR and Western blot were used to detect the mRNA and protein levels of HMGB1, TLR-4, NF-κB, MyD88 and TGF-β in lung tissue from GTS-21 group and irradiation control group at different time after radiation. Results: The result from HE and Masson staining showed that GTS-21 could dramatically reduce radiation-induced lung inflammation and following mitigate lung fibrosis. Then, we found that radiation-induced TNF-α, IL-1β and IL-6 in serum were also inhibited by GTS-21. Comparing to the control group, the mRNA levels of HMGB1, TLR-4 and NF-κB were decreased at the early time of radiation pneumonitis, and the most significant difference was observed at 21d post-irradiation (P<0.05), the mRNA levels of TGF-β was decrease in GTS-21 group at 3m and 6m post-irradiation when compared to control (P<0.05). However, there did not have any different on MyD88 between GTS-21 and control groups. The result from western blot showed that the protein levels of HMGB1, TLR-4 and NF-κB in GTS-21 group were also significantly decreased at 21d after radiation. After 3m and 6m from radiation, the protein level of TGF-β was decreased dramatically at GTS-21 group. Conclusion: GTS-21 can reduce radiation pneumonitis and fibrosis by inhibiting HMGB1/TLR-4/NF-κB pathway which subsequently decrease TGF-β expression.

Keywords: inflammatory cytokines, Radiation-induced lung injury, HMGB1/TLR-4/NF-κB pathway, GTS-21

Poster Session 2 – P2.05: Radiotherapy

P2.05-002 CACNA2D1 Enhances Radio-Resistance in Cancer Stem-Like Cells in NSCLC

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Background: Radiotherapy is one of the most important treatment methods for patients with non-small cell lung cancer (NSCLC). However the presence of radio-resistant cancer stem cells (CSC) may contribute to the relapse or poor outcome of radiotherapy. We previously identified calcium channel α2δ1 subunit (CACNA2D1) isoform 5 as a marker for CSC in hepatocellular carcinoma. This study aimed to investigate the radio-sensitivity of CACNA2D1+ cells in NSCLC cell lines. Methods: NSCLC cell lines A549, H1975 and PC9 were used. CACNA2D1 knockdown or overexpression cell lines were established by lentivirus infection. The proportion of CACNA2D1+ cells before and after radiation was analyzed.
by flow cytometry. Colony formation assay was performed to determine the radiosensitivity. Spore formation assay in serum-free medium was performed to evaluate the self-renewal capacity. YHAX foci were analyzed by immunofluorescence. The monoclonal antibody of CACNA2D1 was applied alone or combined with radiation to CACNA2D1+ cells and colony formation and spore formation assays were performed to determine its effect on CACNA2D1+ cells. Results: CACNA2D1+ cells had higher spore-forming efficiency, and were resistant to radiation compared with CACNA2D1- cells. Increased expression of CACNA2D1 percentage was enhanced after radiation. These data suggest CACNA2D1+ NSCCL cells are relatively radio-resistant. Knockdown of CACNA2D1 in CACNA2D1-high A549 enhanced radiosensitivity, while overexpression of CACNA2D1 in CACNA2D1-low PC9 and H1975 reduced radiosensitivity, suggesting CACNA2D1 converts the radio-resistance. The number of YHAX foci increased after radiation, and decreased more rapidly in CACNA2D1-overexpression cells than control group. Moreover, in CACNA2D1-overexpression cells, the baseline phosphorylation level of CHK2 and ATM was higher than control group, and were more activated after radiation, suggesting CACNA2D1 overexpression resulted in an increase in the DNA damage repair capacity. The monoclonal antibody of CACNA2D1 enhances the radio-sensitivity of CACNA2D1+ cells, suggesting its potential to improve the treatment outcome when combined with radiation on NSCCL.

Keywords: CACNA2D1, NSCCL, Cancer stem cell, radio-resistance

**POSTER SESSION 2 – P2.05: RADIOTHERAPY BIOLOGY – TUESDAY, DECEMBER 6, 2016**

**P2.05-003 PIK3CA MUTATION IS ASSOCIATED WITH INCREASED LOCAL FAILURE IN LUNG STEREOTACTIC BODY RADIATION THERAPY (SBRT)**

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Background: Hyperactivation of the phosphatidylinositol 3-kinase (PI3K) pathway has been associated with radioresistance. It is unclear whether such mutations also confer suboptimal local control for patients who receive lung stereotactic body radiation therapy (SBRT). Our objective was to examine whether mutations in the EGFR/AKT/PI3KCA signaling pathway are associated with local failure after lung SBRT. Methods: We retrospectively reviewed 134 patients who underwent SBRT to primary or metastatic lung lesions from 2007-2015 for whom molecular testing data was available for EGFR, AKT, and PIK3CA genes. For tumors of lung origin (n=122), molecular testing data was included from the lung tumor. For metastatic tumors to the lung (n=12), molecular testing data from either a primary or metastatic tumor site was used. Association between clinical factors, including molecular mutation status, and LF was evaluated with Cox regression analysis. The Kaplan-Meier method was used to assess differences in LF rates based on PIK3CA mutation status. Results: The most common histology was adenocarcinoma (90%) among all tumors. Six patients (4%) had PIK3CA mutation, 31 patients (23%) had EGFR mutation, and one patient (0.7%) had AKT mutation. Median lesion size was 2.0 cm (range, 0.6–5.6 cm), median dose was 48 Gy (range, 30–70 Gy), and median number of fractions was 4 (range, 3–10). Median follow-up was 20 months (range, 0.2–70 months). LF was observed for 16 patients (12%). Median time to local failure was 15 months (range, 7–31 months). On univariate analysis, PIK3CA mutation presence was associated with LF (HR 5.3 [95% CI 1.1–25.0], p=0.03), while tumor histology (adenocarcinoma vs. other), tumor size (<2 cm vs. >2 cm), primary tumor site (lung vs. other), and EGFR or AKT mutation presence were not. By multivariate analysis, PIK3CA mutation trended toward association with LF (HR 3.0 [95% CI 0.25–31.3], p=0.051). At one year, probability of LF in tumors with PIK3CA mutations was 12.4% vs. 5.7% in lesions without mutations (p=0.02). Lesions with PIK3CA mutations were associated with a decreased time to LF (mean 17.9 months [95% CI 12.2–23.2 months]) compared to those without PIK3CA mutations (mean 51.6 months [95% CI 31.2-64.7 months]). Conclusion: We explored EGFR/AKT/PIK3CA pathway mutations and found that patients with PIK3CA mutations are at higher risk for LF after lung SBRT. Due to the limitation of small numbers, this data needs to be validated in a larger patient cohort. Nonetheless, this is a novel finding and hypothesis-generating for future studies.

Keywords: Radioresistance, local failure, PIK3CA, Stereotactic body radiation therapy

**POSTER SESSION 2 – P2.05: RADIOTHERAPY BIOLOGY – TUESDAY, DECEMBER 6, 2016**

**P2.05-004 ABT-737, A BH3 MIMETIC, ENHANCES THERAPEUTIC EFFECT OF IONIZING RADIATION IN MURINE LUNG CANCER MODEL**

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Background: Radiotherapy is one of the main treatment modalities of lung cancer, but its effectiveness is often hampered because of dose dependent radiation toxicity. Aberrations in anti-apoptotic pathways after irradiation is another mechanism attenuating therapeutic effect of radiation. ABT-737, a ‘first-in-class’ of BH3 mimetics, disrupts the BCL-2/BAK complex and initiates BAK-dependent intrinsic apoptotic pathway. In this study, we sought that ABT-737 is able to maximize the therapeutic effects of radiation in experimental animal models.

Methods: Mice were obtained by genotyping of offspring from LSL Kras G12D and p53fl/fl mouse. Lung cancer was induced by inhalation of 5×10⁶ PFU AdCre viral particles at 8 weeks age. After 12 (±2) weeks of irradiation, the mice were randomized and treated with either vehicle or ABT-737 (50 mg/kg, i.p., daily) for 3 days. Then mice underwent microCT and were irradiated in the left lung at a dose of 20 Gy using X-rad 320. In 2 weeks, 2nd round microCT was performed and lungs were harvested for histological analysis. Results: When the changes in the expression of pro-apoptotic and anti-apoptotic molecules after 20 Gy of irradiation were evaluated by immunohistochemistry, the decrease of BCL-2 (like 11, BCL2L11) was most prominent in the irradiated lung. The tumor area was decreased in the irradiated lung of both vehicle and ABT-737 pretreated mice and inhibitory effect was remarkable when the mice were pretreated with ABT-737. Disputed tumor structure with apoptotic bodies were most frequently observed in the irradiated lung of ABT-737 pretreated mice. To quantify the apoptotic effect of this combination, immunohistochemical analysis against activated caspase-3 was performed. Counts of activated caspase-3 were significantly higher in the irradiated lung with ABT-737 pretreatment, suggesting ABT-737 possesses radiosensitizing property. Conclusion: Decrease of BCL2L1 expression in the irradiated lung is one of prominent findings, which might compromise therapeutic effect of radiation. Pretreatment of ABT-737 enhanced anti-tumor effect of ionizing radiation in Kras-p53fl/fl lung cancer model, suggesting BH3 mimetics would be a good candidate of radiosensitizer in lung cancer. Further studies are warranted for identification of optimal dosing and schedule of this combination treatment.

Keywords: apoptosis, radiosensitizer, BH3 mimetics, ABT-737

**POSTER SESSION 2 – P2.05: RADIOTHERAPY BIOLOGY – TUESDAY, DECEMBER 6, 2016**

**P2.05-005 MECHANISM OF RADIOTHERAPY IN REDUCTION/DELAY OF T790M-MEDiated EGFR TKI RESISTANCE**

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Background: EGFR T790M mutation accounts for more than 50% of acquired resistance to TKI. In pre-clinical, EGFR-TKI resistant cells with T790M exhibited enhanced sensitivity to radiation, suggesting the potential of radiotherapy in reduction and delay of T790M-mediated EGFR TKI resistance. Methods: Under different radiation dose and times, we used droplet digital PCR to observe the emerging time of T790M and its proportion during chronic exposure to gefitinib in TKI-sensitivity cell lines, and to evaluate the anti-tumor effect of early radiation combined with gefitinib in xenograft model with different proportion of T790M. Furthermore, we performed mRNA microarray to screen mRNAs differentially expressed in the paired NSCLC gefitinib-sensitivity cell lines and gefitinib resistant cell lines and find potential molecular markers of T790M mutation. Results: Our data showed radiation combined with gefitinib delayed the occurrence of EGFR T790M mutation compared to gefitinib alone in T790M wildtype (TKI-sensitive) cell lines. It also reduced the T790M mutation abundance in novo T790M mutation (TKI-resistant) cell line. The phenomena was also confirmed in mice xenograft model. In addition, our results showed TKI-resistant (induced T790M mutation) cells had higher radiosensitivity than TKI-sensitive cells. mRNA array showed mir-1275 was the one of the most significantly elevated mRNAs in TKI-resistant cells. Knockdown of miRNA-1275 significantly decreased the radiosensitivity of TKI-resistant cells. Western blot showed...
**Abstracts**

knockdown of miR-1275 affected proteins relating to cell proliferation and apoptosis. Bioinformatics showed SPDOCK1 might be one of the targets of miRNA-1275. Conclusion: Our results contribute to understand molecular mechanisms of T790M-mediated EGFR-TKI resistance, but also provide a new therapeutic strategy for patients in advanced NSCLC to aid expansion of the effectiveness of TKI treatment through radiotherapy.

Keywords: EGFR-TKI, Acquired resistance, radiation, T790M

**POSTER SESSION 2 – P2.05: RADIOTHERAPY**

**Clinical Outcome – TUESDAY, DECEMBER 6, 2016**

**P2.05-006 RADIOTHERAPY AS DEFINITIVE TREATMENT IN PATIENTS AGED 70 YEARS AND OLDER WITH NON-SMALL CELL LUNG CANCER**

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Background: The factors affecting survival were evaluated in patients aged ≥70 years with non-small cell lung cancer (NSCLC) treated with definitive radiotherapy (RT). The methods: Between January 1996 and April 2012, 52 patients were treated. The median age was 73 (range: 70–80), 73% and 75% of patients with stage III according to AJCC 2002 and 2010, respectively. RT was performed median 6160 cGy (range: 3600–6600) and chemotherapeutic agents (CHEM) were given 75% of the patients as neoadjuvant, concurrent or adjuvant. Statistical analysis was calculated with Kaplan-Meier and Cox regression methods. Results: Median follow-up was 12.5 months (range: 2.5–103). Median overall (OS), disease-free (DFS) and locoregional-progression-free (LRPFS) survival were 22 (95% CI 12.9–31.1), 18.5% (95% CI 7.2–39) and 25 months (95% CI 15–34), respectively. Two-year OS, DFS and LRPFS rates were 50%, 47% and 52%, respectively. Acute ≥ Grade 3 esophagitis and neutropenia were seen 6% and 10% of patients. Whereas the mortality associated with CHEM were seen of 5 (10%) patients, RT-related death was not observed. In univariate analysis, AJCC 2002 stage III (72 vs 20 months, p = 0.05), RT dose ≥ 60 Gy (27.5 vs 12.5 months, p = 0.01), RT duration > 49 days (31 vs 11 months, p < 0.01) for OS and RT dose ≥ 60 Gy (25 vs 11 months, p = 0.02), RT duration > 49 days (26.5 vs 10.5 months, p < 0.001) neoadjuvant CHEM ≤ 3 cycles (mean 58 vs 19 months, p = 0.03), complete response (72.5 vs 18.5 months, p = 0.03), ≥ 4 cycles of CHEM (25 vs 11 months, p = 0.05) for DFS were significant. In multivariate analysis, RT duration > 49 days were found a positive impact on OS (HR: 3.235, 95% CI: 1:25 vs 11 months, p = 0.05) for DFS were significant. In multivariate analysis, RT dose and number of fractions were significant. Conclusion: The treatment outcome of SBRT / PBT was equivalent to that of WR, SBRT / PBT may be alternative treatment in stage I NSCLC high risk patients.

Keywords: SBRT, Surgery, lung cancer

**P2.05-008 CAN STEREOTACTIC BODY RADIATION THERAPY (SBRT) BE AN EFFECTIVE TREATMENT FOR LUNG METASTASES FROM “RADIORESISTANT” HISTOLOGIES?**

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Background: Metastasis from “radioresistant” histologies are commonly regarded as less responsive to SBRT. Almost no data are available in Literature to evaluate the impact of these histologies on the outcome of patients with lung metastases treated with Stereotactic Body Radiation Therapy (SBRT). Therefore, we conducted this analysis on patients with lung metastases from renal cell carcinoma, hepatocellular carcinoma, adenoid cystic carcinoma and melanoma treated with SBRT at our Institution. Methods: Oligometastatic patients with lung metastases from renal cell carcinoma, hepatocellular carcinoma, adenoid cystic carcinoma and melanoma who received SBRT and with a discrete follow up time were included in this analysis. Kaplan Meyer analysis was used to calculate Overall Survival, Progression Free Survival, Local Control. Crude rates were used to calculate the response and distant failure rates. Toxicity was scored according to CTCAE v. 4.03 Results: Forty patients were included in the study. Most common primary histologies were renal cell carcinoma and hepatocellular carcinoma. Most of patients had 1 or 2 metastatic sites. Half patients did not receive any systemic therapy during their history before SBRT. Different RT doses and number of fractions were utilized according to site, number and volume of lung metastases, 48 Gy in 4 fractions was the most commonly prescribed schedule. The best local responses obtained were complete response in 13 patients (21.7%), partial response in 28 patients (46.7%) and stable disease in 14 patients (23.3%). For oligometastatic patients (8.3%) had a local failure of 9 months. With a median follow-up of 24.3 months (range 4.1–118.6 months), local control was 93.7% and 86.1% at 1 and 2 years respectively. OS and PFS at 1 and 2 year were 89.5%, 64.6%, 87.7% and 70.1%, respectively. None of the analyzed parameters showed a statistically significant impact on any outcome. Treatment was well tolerated. None but 5 patients experienced acute toxicity of any grade. During follow up in 10 cases G1-2 toxicity (mostly pneumonia) were recorded. Conclusion: SBRT for lung metastases is an effective treatment for oligometastatic patients with lung metastases from “radioresistant” histologies. The treatment is safe and well tolerated and the outcomes are equivalent to the results obtainable with SBRT for lung metastases from more favourable histologies.

Keywords: Stereotactic body radiation therapy, Oligometastases, Radioresistance, lung metastases

**POSTER SESSION 2 – P2.05: RADIOTHERAPY**

**CLINICAL OUTCOME – TUESDAY, DECEMBER 6, 2016**

**P2.05-009 THE OUTCOME AND ADVERSE EVENT OF CHEMORADIATION + SURGERY FOR STAGE III NON-SMALL CELL LUNG CANCER**

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2Radiation and Proton Beam Therapy Center, Shizuoka Cancer Center, Shizuoka/Japan
3Shizuoka Cancer Center, Shizuoka/Japan, 4Thoracic Oncology, Shizuoka Cancer Center, Shizuoka/Japan, 5Clinical Research Center, Shizuoka Cancer Center, Shizuoka/Japan

Background: Recently, excellent results of stereotactic body radiotherapy (SBRT), proton beam therapy (PBT) for stage I non-small cell lung cancer (NSCLC) have been reported, however any phase III trial comparing SBRT and surgery have not been completed yet. The aim of this study is to compare outcomes between SBRT, PBT and wedge resection (WR) for patients with peripheral stage I NSCLC who intolerable for anatomical resection, and analyze prognostic factors in this population. Methods: We retrospectively compared overall survival (OS), local recurrence rate (LRR), relapse-free survival (RFS) and cause-specific survival (CSS) between WR (n=172) and SBRT / PBT (n=188) for pathologically proven clinical stage I NSCLC in our institute from 2002 to 2015. Patients who underwent WR were all high risk patients who intolerable for anatomical resection and achieved complete resection without any adjuvant therapy. Of radiation group (RT: SBRT+PBT), 56% was medically inoperable, with 44% refusing surgery. SBRT, 60 Gy in 8 fractions, PBT, 60-80 Gy in 10-20 fractions was prescribed. Propensity score matching was used to adjust the confounding effects in estimating treatment hazard ratios. 59 WR patients and 59 radiotherapy (RT) patients (SBRT 27, PBT 32) were matched blinded to outcome (1:1 ratio). There were 70 men and 48 women, median age was 81, and median follow-up period was 39 months. Results: 3-, 5-year overall survival (OS) of WR and RT was 84.5%, 70.8% vs 89.7%, 59.6% (p = 0.802), respectively. 3-year LRR, RFS, CSS were 94.7% vs 95.9% (p = 0.751), 87.5% vs 75.6% (p = 0.351) and 91.2% vs 93.9% (p = 0.875), respectively. Multivariate analysis of prognostic factors for OS demonstrated any factors including treatment modality were not significant. Conclusion: Our results suggest that the treatment outcome of SBRT / PBT was equivalent to that of WR, SBRT / PBT may be alternative treatment in stage I NSCLC high risk patients.

Keywords: SBRT, Surgery, lung cancer

This abstract has been corrected to add the correct authors' affiliations.
Background: Concurrent chemoradiation therapy (CRT) is standard for stage III non-small cell lung cancer (NSCLC). In our institute, patients undergo surgery after CRT if possible. We aimed to assess the efficacy and adverse event of CRT in patients with stage III NSCLC and investigate the risk of radiation pneumonitis (RP). Methods: Two hundred fifty seven patients received CRT for newly diagnosed stage III NSCLC from 2003 to 2013. Patient characteristics were as follows: 87.2% male; median age, 67 years; 55.6% stage IIIA; and 44.4% IIIb. CRT was prescribed, with 40Gy to the primary tumor and mediastinum and a boost of 20Gy to all gross disease. All patients also received platinum based doublet regimen concurrently. After CRT, the patients were re-evaluated in the resectability and underwent surgery. We analyzed tumor volume reduction ratio near the end of radiation therapy. All patients were classified by their lung condition about emphysematous and interstitial changes with CT images before treatment into three degree (slight / moderate / severe). Patients with grade 2 or worse RP were evaluated with their Dose-Volume Histogram (DVH) parameters of both lungs. Results: The median follow up time was 73.9 months. The 3-year and 5-year overall survival rates were 44.8 % and 33.0 % in all patients, and 74.7 % and 64.7 % in patients with CRT followed by surgery. The 3-year and 5-year local control rates were 68.8 % and 40.0 %, respectively, in all patients. More than 50 % volume reduction was observed in 73.2 % of patients surviving over 2-years, but 32.3 % of these good responder had local failure. Grade 2 or worse RP were observed in 70 patients (27 %), grade3 in 11 patients (4 %), grade 5 in 3 patients (1 %). The median of V5Gy, V10Gy, V20Gy, V40Gy, and mean dose of group with grade 2 or worse RP were 32.1, 27.5, 22.5, 16.5, 13, and 13.5Gy, respectively, and in grade 3RP with grade 3 to 5 RP were 31.5, 27.9, 23.9, 19.0, and 12.8,Gy respectively. In patients with grade 3 to 5 RP, 8 of 14 patients had severe emphysematous lung and moderate or severe interstitial change, or had over 30 % lung V20Gy. Conclusion: CRT for stage III NSCLC was effective with acceptable toxicities. Even though patients had good early response to CRT, local control was not sufficient. Grade 3 or worse RP may relate not only to DVH parameters, but also pulmonary complication before CRT.

Keywords: CRT, lung cancer

Poster Session 2 - P2.05: Radiotherapy Clinical Outcomes - Tuesday, December 6, 2016

P2.05-010 STEREOTACTIC RADIOACTIVITY THERAPY (SBRT) FOR PRIMARY AND METASTATIC LUNG TUMORS IN ELDERLY PATIENTS

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Background: To evaluate SBRT for primary and metastatic lung tumors in elderly patients. Methods: Retrospective analysis of technique and results of SBRT for lung tumors in patients over 75 years old treated in a single institution.

Simulation was made with CT, abdominal compression and stereotactic frame. Internal target volume (ITV) was covered according ICRU recommendations. Treatment delivery using planar or noncoplanar fields or VMAT-IMRT dynamic arc. The prescribed dose was either 3 fractions of 15 Gy each or a single 30 Gy fraction. Planar images or cone beam CT were used for verification. Toxicity and radiologic response were assessed using standardized criteria (RTOG and RECIST). Survival rates and toxicities were calculated by the Kaplan-Meier method. Results: Between 2002 and 2015, 86 patients had 103 SBRT procedures; of those 66 were for primary lung tumors (T1-2N0M0) and to procedures; of those 66 were for primary lung tumors (T1-2N0M0) and to

S543
Between 2010 and 2015, 68 patients were treated with radiation therapy alone. Most of patients were male and white. The median age at diagnosis was 60.22 years. AJCC Stage III disease was the most prevalent one. The median survival for all stages was 8,005 months (95% CI 5,796 to 10,313 months). Overall survival at 5 years was 17.7%. Conclusion: Radiotherapy alone resulted in very poor survival in this cohort. Our data is original in Brazil. Most of lung cancer patients who may not tolerate surgery or a chemoradiation regime die. New alternatives for the management of these patients are necessary.

Keywords: definitive radiotherapy, lung cancer

Patient characteristics

<table>
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<tr>
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<tbody>
<tr>
<td>Age, (Mean)</td>
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</tr>
<tr>
<td>Gender, No. (%)</td>
<td>Men Women</td>
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</table>

Between 2010 and 2015, 68 patients were treated with radiation therapy alone. Most of patients were male and white. The median age at diagnosis was 60.22 years. AJCC Stage III disease was the most prevalent one. The median survival for all stages was 8,005 months (95% CI 5,796 to 10,313 months). Overall survival at 5 years was 17.7%. Conclusion: Radiotherapy alone resulted in very poor survival in this cohort. Our data is original in Brazil. Most of lung cancer patients who may not tolerate surgery or a chemoradiation regime die. New alternatives for the management of these patients are necessary.

Keywords: definitive radiotherapy, lung cancer

Poster Session 2 - P2.05: Radiotherapy

Clinical Outcome - Tuesday, December 6, 2016


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Background: Stereotactic brain radiosurgery (SRS) was demonstrated to provide good local control in patients with oligo-brain metastases (commonly defined as 4 or less). The discovery of different targeted therapies provided significant improvement in survival in the past decade. We reviewed the effectiveness of SRS in lung cancer patients with oligo-brain metastases and identified prognostic factors which potentially can aid better patient selection and improved outcomes for patients with brain metastases treated with SRS in Prince of Wales Hospital, Hong Kong in Jan 2010–July 2015 were reviewed. Outcomes including local control rate (LCR), distant brain control rate (BCR) and overall survival (OS) were analyzed. Prognostic factors were identified with univariate and multivariate analyses. Correlation with available prognostic scorings including RTOG Recursive Partitioning Analysis, Basic Score for Brain Metastases, the Score Index for Radiosurgery and Graded Prognostic Assessment was evaluated. Results: Forty-eight patients with 66 lesions were treated with LINAC-based SRS with single dose of 12–24 Gy (median dose 18.6Gy). The distribution of different subtypes is as follows: Non-small cell lung cancer (NSCLC)/adenocarcinoma NOS n=18 (37.5%), EGFR mutation n=17 (35.4%), ALK IHC+ n=3 (6.3%), adenocarcinoma of unknown n=2 (4.2%), squamous cell carcinoma n=5 (10.4%), small cell carcinoma n=2 (4.2%) and unknown subtype n=1 (1.8%). The median follow up time was 11.0 months (0.4–71.4 months). Five patients (9.4%) were symptomatic with acute brain edema. Seven patients (14.6%) had delayed seizure after a mean time of 10.1 month (2.0-33.5 months). Six patients (12.5%) became steroid dependent. The median OS was 13.0 months. One year actuarial LCR was 73% and distant BCR was 67%. OS correlated significantly with all four scoring systems. Among NSCLC patients, those with activating EGFR mutation (exon 19 deletion or exon 21 L858R mutation) (n=12) had superior OS compared with non-mutational group (p=0.036, HR 2.811 95% CI 1.072-7.369), but there was no statistically significant difference on local or distant brain control. Concomitant whole brain radiotherapy (WBRT) did not significantly affect OS, local and brain control in the whole group and in EGFR activating mutant subgroup. Conclusion: SRS provided good control in patients with primary lung cancer with oligo-brain metastases. Current available prognostic scores provide good estimation of survival. Patients with EGFR activating mutation had superior survival after SRS compared with non-mutational NSCLC group.

Keywords: Oligo-brain metastases, Stereotactic Radiosurgery, Lung Cancer, EGFR activating mutation

Poster Session 2 – P2.05: Radiotherapy

Clinical Outcome - Tuesday, December 6, 2016

P2.05-014 Sites of Recurrent Disease in SCLC Patients Treated with Radiochemotherapy - Is Selective Nodal Irradiation Safe?

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Background: Concurrent radiochemotherapy (CCRT) is the standard treatment in locally advanced small cell lung cancer (SCLC) patients. Even though elective nodal irradiation (ENI) had been advocated, its use in routine clinical practice is still limited [1]. Therefore, the purpose of this study is to assess the sites of recurrent disease in SCLC patients and to evaluate the feasibility of selective nodal irradiation (SNI) versus ENI. Methods: A retrospective single-institution study was performed in stage I-II SCLC patients treated with CCRT. After state-of-the-art staging, all patients underwent three-dimeional conformal radiotherapy to a total dose of 45 Gy in twice-daily fractions of 1.5 Gy starting concurrently with the first or second chemotherapy cycle (etoposide, cisplatinum). The gross tumor volume (GTV) consisted of the primary tumor and SNI visualized on CT and/or FDG-PET, or confirmed by cytology. The clinical target volume (CTV) was obtained by expanding the GTV, adjusting it for anatomical boundaries, and electively adding the supraclavicular lymph nodes. After the CTV was expanded to a planning target volume based on institutional guidelines. After CCRT, prophylactic whole-brain irradiation (WBI; 30 Gy in 15 fractions) was administered to patients with a (near-complete) response. Follow-up consisted of a CT-thorax 6-8 week after completing treatment, followed by a 3-monthly chest x-ray or CT-scan. For this retrospective analysis, we reviewed all imaging data used for radiation treatment planning and during follow-up. The site of loco-regional relapse was correlated to the initial site and dose delivered. Results: Between April 2004 and December 2013, 54 patients underwent CCRT (followed by WBI in 63%). After a median time of 11.5 months, 17 patients (31.5%) had radiologic locally or regionally: six within the initial primary tumor volume, five within the initially affected lymph nodes, three metachronously within the primary tumor and initially affected lymph nodes, and three inside but outside of the initial nodal disease. Only one patient developed isolated supraclavicular lymph node metastases in the electively treated volume. All sites of loco-regional recurrence had received 92%-106% of the prescribed dose. Thirty-seven patients (69%) developed distant metastases (37.8% liver, 35% brain). Conclusion: In this retrospective analysis, most patients recurred in the initially affected primary tumor or lymph nodes, or distantly. So, in order to reduce toxicity and potentially increase dose in GTV/CTV, one may consider omitting irradiation of the supraclavicular lymph node metastases in those patients with affected lymph nodes in the lower hilar and mediastinal lymph node stations.

Keywords: SCLC, Radiochemotherapy, Enthusiastic, Safe

Poster Session 2 – P2.05: Radiotherapy

Clinical Outcome - Tuesday, December 6, 2016

P2.05-015 Long-term Outcomes of Prospective Phase I Clinical Trial for Stereotactic Ablative Radiation Therapy in Recurrent NSCLC

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Background: To evaluate the long-term efficacy, pattern of failure, and toxicity of stereotactic ablative radiotherapy (SABR) for recurrent or multiple primary non-small-cell lung cancer (NSCLC). Methods: Patients
with histologically confirmed, 18F-fluorodeoxyglucose (18F-FDG)-PET staged, recurrent or multiple primary NSCLC, suitable for SABR (<5 cm, not abutting critical structures, met with SABR dose volume constraints), were prospectively enrolled and treated with volumetric image-guided SABR to 50 Gy in 4 fractions (prescribed to planning target volume). Lobar recurrent disease was defined as recurrence in the same lobe with the same histology after definitive therapy from prior NSCLC (n=16); synchronous tumors was defined as with two early stage NSCLC in the different side (n=3). Four-dimensional computed tomography (4DCT) was used for simulation and planning. Patients were followed with CT or PET/CT every three months for two years, then every 6 months for three years and then annually. Results: From February 2006 to April 2013, 63 patients were enrolled and eligible for evaluation. The median age was 70 years (range 45-86) and median follow-up was 4.2 years (the interquartile range 3.0-7.3 years). A total of 5 (7.9%) patients developed cumulative actual local recurrence within PTV and 18 patients (28.6%) developed any cumulative actual recurrence (local, regional and distant) after SABR. Estimated total local failure rates in the same lobe at 3-, 5-year were both 11.2% (95% CI 6.8-15.6). Estimated 3-, 5-year PFS rates were 60.2% (95% CI 53.7-66.7) and 52.8% (95% CI 43.5-61.7), respectively; corresponding overall survival rates were 64.1% (95% CI 58.0-70.2) and 52.6% (95% CI 43.5-61.7), respectively; corresponding overall survival rates were 64.1% (95% CI 58.0-70.2) and 52.9% (95% CI 45.5-60.3). Three (4.8%) patients developed grade 3 treatment-related adverse events (one [1.6%] dermatitis, one [1.6%] chest wall pain, and one [1.6%] radiation pneumonitis). No patient had grade 4 or 5 event. Conclusion: This exploratory prospective study showed excellent 5 years local control, minimal toxicity and outstanding 5 years OS and PFS for recurrent or multiple primary NSCLC treated with SABR, indicating a potential cure for some patients. Close follow up and surveillance after initial definitive treatment should be considered to detect early recurrence in NSCLC.

Keywords: Recurrent non-small cell lung carcinoma, Stereotactic Ablation Radiotherapy, clinical trial, stereotactic body radiotherapy

P2.05-016 HIGHER DOSE OF RADIOTHERAPY BETTER FOR OUTCOME OF PATIENTS WITH LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER
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Background: The standard treatment for inoperable locally advanced non-small cell lung cancer (LA NSCLC) includes concurrent or sequential chemoradiotherapy and radiation therapy (RT). RT with 60 to 66 Gy in 30-33 fractions represents a backbone of treatment in inoperable LA NSCLC and optimal radiation dose is essential for successful treatment. Long-term survival rates with these approaches remains in the order of 15–20%. Methods: We evaluated the clinical significance of the RT doses in patients with inoperable LA NSCLC who underwent concurrent chemoradiotherapy in our institution between 2005 and 2010 and correlated the doses with outcome of treatment. All patients were treated with three 21-day cycles of induction chemotherapy with cisplatin and gemcitabine. Within 13 – 22 days after the last application of chemotherapy, all patients continued treatment with conventionally fractionated 3D-RT in 2 Gy fractions concurrently with cisplatin and etoposide. We evaluated the outcome of the patients treated with RT doses less or equal 62 Gy and treated with more than 62 Gy. Results: One hundred and five patients were treated with combined chemoradiotherapy between 2005 and 2010 in our institution, 82 males and 23 females. Most patients had surgically inoperable tumor in stages IIIA (50 patients) and IIIB (51 patients), 4 patients were medically inoperable. The most predominant histological subtype was squamous cell carcinoma (75%), followed by adenocarcinoma (15%). No statistical significant differences in patient characteristics, including age, smoking status, gender and histology were found according to the dose of RT. The dose intensity of induction and concurrent chemotherapy, expressed as a mean percentage of prescribed drug administered, was not statistically different for any drug used according to the dose of RT. Radical irradiation with doses of 54–62 Gy and 62.1–66 Gy was completed in 47 and 58 patients. After a median follow up of 103.4 months, 17 patients were still alive, 11 patients treated with ≤62 Gy. Median overall survival (mOS) was 16.6 and 31.4 months for RT doses ≤62 Gy and > 62 Gy, respectively (p = 0.037). (Fig. 1). 5-years survival was 19.1% and 29.3% for treatment with ≤62 Gy and > 62 Gy. Conclusion: RT dose may be an important factor for outcome of patients with LA-NSCLC. Our analysis confirms the importance of RT dose on outcome in patients with LA NSCLC, but since small number of patients were included, no firm conclusion could be made and further clinical investigation is warranted.

Keywords: Locally advanced NSCLC, dose of radiotherapy

P2.05-017 TUMOR REGRESSION GRADE PREDICTS DISEASE FREE SURVIVAL
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Background: Tumor regression during chemoradiation (CRT) in stage III non-small cell lung cancer patients has been described. Our aim was to investigate whether the extent of the primary tumor shrinkage is associated with local control and survival. Methods: Changes in the volume of the primary tumor (GTv7 T) of 41 patients treated with concurrent (cCRT) (n=21) or sequential (sCRT) (n=20) CRT were analyzed using cone-beam CT (CBCT) at every fifth fraction (F5–F30). Only changes in the primary tumor (excluding the lymph nodes) were considered. Previous research revealed F15 and F20 as optimal timing for treatment adaptation for cCRT and sCRT respectively (Berkovic et al. Acta Oncol 2015). Local control and survival data were reviewed retrospectively. Impact of the tumor regression at the time of the optimal adaptation timing during treatment (higher or lower than median) and chemotherapy schedule (cCRT vs. sCRT) on local control and survival were evaluated using the Kaplan-Meier survival comparison (log-rank test, p<0.05 were considered significant). Results: Median local control (LC) and overall survival (OS) was 32.5 res. 29.9 months in the sCRT and 31.4 res. 23.3 months in the cCRT group. LC and OS did not differ significantly for the cCRT and sCRT cohort. The median GTv7 radiation treatment was 35.0% (range 2.8–64.2%) at F15 for cCRT, while 21.9% (2.1-53.5%) at F20 for sCRT patients. Higher than the group median for cCRT and sCRT GTv7 radiation reduction showed statistically significant impact only on disease specific survival (p=0.016, Figure 1). Conclusion: Higher gradient GTv7 reduction during CRT significantly correlates with better disease specific survival. Additional tumor and patient characteristics should be studied in larger patient cohorts to further understand tumor behavior and to offer a validated predictive tool of therapeutic outcomes. Figure 1. Kaplan-Meier survival curve for DSS.
Abstracts

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Background: Isolated intrathoracic relapse is common across distinct tumors and especially in lung cancer. Patients who received previous radiotherapy treatment (PRT) are not suitable for salvage surgery and chemotherapy provides poor local control. This study aimed to assess the toxicity and outcome of SBRT re-irradiation (reRT) in patients with solid tumors who developed an intrathoracic relapse. Methods: 35p treated with PRT who received salvage SBRT were identified in our database and their medical records were retrospectively reviewed. All patients underwent complete pulmonary function tests (cPFTs) (including DLO, FEVI and FVC) and PET-CT scan was performed before and after receiving lung reRT. Treatment planning was performed using the reirradiation treatment plan and calculating the cumulative total nominal dose. Survival estimations were performed using Kaplan-Meier and differences between PFTs prior and post-reRT were analyzed using Student T-Test. Early toxicity was defined when it occurred up to 6 months. Results: Median age: 68 (53-81); 23p (83%) were male The previous treatments: SBRT in 17p (49%), 3D-RT a p (11%) and CT-RT 14p (40%) Mean RT dose 60,4Gy (34-74). Primary tumors: lung 24 (65%), colorectal 9 (25%), oesophagus 2 (6%). For lung cancer, the stage distribution was: IA 8 (23%), IB 2 (6%), II A 2 (5.7%), II B 3 (1%), III A 4 (5%), IIIB 1 (1%), IV (2%). For other primaries 13 (38%) were non metastatic at diagnosis and developed oligoprogressive disease in thorax which was treated with SBRT and 3 (8.5%) were oligometastatic. The location of reRT site: same lobe 17 (48%), ipsilateral different lobe 7 (20%), contralateral lobe 11 (32%). Median delivered dose of salvage SBRT was 50Gy (50-60) in 10 fractions (3-10). Median accumulated dose in the baseline and post re-irradiation PFTs were: FEVI, FVC and DLCO difference and CI% were 2.41 (-1.79-6.62); 65 (-125-257) and 12.5 (-91-121). Asthenia 68 in 12p (31%) was the most frequent late toxicity, no long term toxicities were detected. Conclusion: Salvage SBRT for treating isolated intrathoracic relapses achieved an outstanding local control and overall survival in selected p. This treatment did not impair post-re-irradiation PFT and long-term toxicities were not observed.

Keywords: SBRT; Reirradiation

P2.05-019 STEREOTACTIC BODY RADIOTherAPY (SBRT) FOR CENTRAL LUNG TUMORS: THE EXPERIENCE OF UNIVERSITY-CAREGGI HOSPITAL RADIOTHERAPY

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Background: Stereotactic body radiotherapy (SBRT) for central lung tumors, defined as tumor within 2 cm or touching the zone of the proximal bronchial tree or tumors immediately adjacent to the mediastinal or pericardial pleura (Adelbar S. et al. BJR 2015) is debated because of toxicities to organs at risk. No evidences from phase III trial are available. Methods: From 2010 to 2015, 45 central lung lesions in 40 pts were treated with SBRT. 14 lesions were primary lung cancer (PLC), 31 were lymphoadenopathies (LAP). PLC were treated with SBRT in 12 cases, with IMRT (step and shoot) in 10 and VMAT in 10. No differences in type B planning algorithm were observed. Planning target volumes (PTV) were calculated using the previous treatment plan and calculating the cumulative total nominal dose. Survival estimations were performed using Kaplan-Meier and differences between PFTs prior and post-reRT were analyzed using Student T-Test. Early toxicity was defined when it occurred up to 6 months. Results: Median age: 68 (53-81); 23p (83%) were male. The previous treatments: SBRT in 17p (49%), 3D-RT a p (11%) and CT-RT 14p (40%). Mean RT dose 60,4Gy (34-74). Primary tumors: lung 24 (65%), colorectal 9 (25%), oesophagus 2 (6%). For lung cancer, the stage distribution was: IA 8 (23%), IB 2 (6%), II A 2 (5.7%), II B 3 (1%), III A 4 (5%), IIIB 1 (1%), IV (2%). For other primaries 13 (38%) were non metastatic at diagnosis and developed oligoprogressive disease in thorax which was treated with SBRT and 3 (8.5%) were oligometastatic. The location of reRT site: same lobe 17 (48%), ipsilateral different lobe 7 (20%), contralateral lobe 11 (32%). Median delivered dose of salvage SBRT was 50Gy (50-60) in 10 fractions (3-10). Median accumulated dose in the baseline and post re-irradiation PFTs were: FEVI, FVC and DLCO difference and CI% were 2.41 (-1.79-6.62); 65 (-125-257) and 12.5 (-91-121). Asthenia 68 in 12p (31%) was the most frequent late toxicity, no long term toxicities were detected. Conclusion: Salvage SBRT for treating isolated intrathoracic relapses achieved an outstanding local control and overall survival in selected p. This treatment did not impair post-re-irradiation PFT and long-term toxicities were not observed.

Keywords: SBRT; Reirradiation

P2.05-020 SURVIVAL OUTCOMES IN STAGE 1 NSCLC FOLLOWING STEREOTACTIC ABLATIVE RADIOTHERAPY OR CONVENTIONAL RADIOTHERAPY

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Background: Stereotactic ablative radiotherapy (SABR) is a radiotherapy technique using ultra-hypofractionated treatment to deliver a high biological dose to early stage lung cancers. It is believed that SABR is more effective than conventional fractionated external beam radiotherapy (EBRT), however definitive evidence of superior survival outcomes from controlled trial comparisons is lacking. Across the UK access to SABR is not uniform, with only certain centres delivering the technique. Before the introduction of a routine SABR service in 2013, patients from Northern Ireland were referred to English centres to have SABR. We compare the outcomes of those patients who had SABR to those who had conventional fractionated radiotherapy for early stage lung cancer. Methods: Using our institutional electronic database, which includes all patients who had radiotherapy in the treatment of lung cancer, we identified those patients who had received SABR or who were eligible to receive it based on UK consortium guidelines (tumor size ≤ 4cm, tumor ≤ 2cm from main airways, performance status 0-3). The time period of 2009 to 2015 inclusive was chosen as SABR treatment was funded from this time point onwards. Patient baseline demographics, lung function, tumor size, the reason for the treatment received, details of the treatment received (e.g. dose, use of respiratory compensation, IGRT and Type B planning algorithm) and survival outcomes were recorded for each patient. Results: Between 2009 and 2015, eighty patients received SABR and an additional 63 were eligible to have SABR but received conventional EBRT (62 patients received SGy in 20 fractions and 1 patient received 66Gy in 33 fractions). The main reason for eligible patients not receiving SABR was that the patient did not want to travel or was not fit to travel to another country to have treatment with SABR (43% of all non-SABR patients). The 2-year overall survival for those receiving SABR was 68% versus 43% for those receiving conventional radiotherapy (HR 2.3 [95% CI 1.4 – 3.8], p=0.0007). Both disease free survival and metastasis free survival rates were superior in the SABR group. On univariate analysis of the various patient and treatment factors, only tumor size remained significant between the groups. Conclusion: In this cohort of patients there is evidence of improved local control, disease free survival and overall survival for SABR compared to conventional fractionated radiotherapy. SABR should be available in all radiotherapy centres for the treatment of early stage lung cancer.

Keywords: SABR, NSCLC, Radiotherapy, stereotactic

P2.05-021 STEREOTACTIC RADIOSURGERY FOR BRAIN METASTASIS IN NON-SMALL CELL LUNG CANCER: PREDICTOR OF INTRACRANIAL PROGRESSION

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POSTER SESSION 2 – P.05: RADIOTHERAPY

CLINICAL OUTCOME

TUESDAY, DECEMBER 6, 2016
Background: Stereotactic radiosurgery (SRS) has been introduced for small-sized single and oligo-metastases in the brain. The aim of this study is to assess treatment outcome, efficacy, and prognostic variables associated with survival and intracranial recurrence. Methods: This study retrospectively reviewed 123 targets in 64 patients with non-small cell lung cancer (NSCLC) treated with SRS between January 2006 and December 2012. All patients underwent SRS with 2000–3000 cGy/1–3 fx for each brain metastasis as a initial treatment or salvage treatment for recurrence after whole brain RT. Median target number and size were 2 targets and 1cm in diameter. Every patient was evaluated according to Eastern Cooperative Oncology Group (ECOG) performance status, RPA class, number and size of brain metastases and other systemic metastases/disease status before SRS. We evaluated overall survival (OS), local tumor control and intracranial progression free survival rate (IPFS) of patients. We also evaluated quality of life immediate after SRS. Treatment responses were evaluated using magnetic resonance imaging. Results: The median follow-up was 13.9 months. The median OS and IPFS were 14.1 and 8.9 months, respectively. Fifty-seven patients died during the follow-up period. The 5-year local control rate was achieved in 85% of 108 evaluated targets. The 1- and 2-year OS rates were 55% and 28%, respectively. On univariate analysis, primary disease control (p < 0.001), the Eastern Cooperative Oncology Group (ECOG) performance status (0 or 1 vs. 2, p = 0.002), recursive partitioning analysis class (1 vs. 2, p = 0.001), and age (65 vs. 65 years; p = 0.036) were significant predictive factors for OS. Primary disease control (p = 0.041) and ECOG status (p = 0.017) were the significant prognostic factors for IPFS. Four patients experienced radiation necrosis and no other severe toxicity was registered within 1 follow-up duration. Conclusion: SRS is a safe and effective local treatment for brain metastases in patients with NSCLC. Uncontrolled primary lung disease and ECOG status were significant predictors of OS and intracranial failure. SRS might be a tailored treatment option along with careful follow-up of the intracranial and primary lung disease status. Omission of WBRT can be option for patient with primary disease controlled and better ECOG with close image follow up.

Keywords: SRS (Stereotactic radiosurgery), Intracranial control, Brain metastasis, non-small cell lung cancer

P2.05-023 PATTERNS OF FAILURE AFTER ADJUVANT RADIATION THERAPY BASED ON “TUMOR BED WITH MARGIN” FOR STAGE III THYMIC EPITHELIAL TUMOR

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Background: This study was conducted to assess optimal radiation target volume in patients with locally advanced thymic epithelial tumor (TET) treated by surgery and postoperative radiation therapy (PORT). Methods: The records of 54 patients with Masaoka-Koga stage III TET, who received surgical resection at Samsung Medical Center, from Jan. 2000 to Dec. 2014, were retrospectively reviewed. The most common TNM stage was T3N0M0 (n=46, 85.2%) according to the new staging system proposed by the International Association for the Study of Lung Cancer and the International Thymic Malignancy Interest Group. The median PORT dose was 54 Gy in 27 fractions. Target volume was confined to the primary tumor bed only, while did not include the regional lymphatics nor pleuro-pericardial space electively. The clinical outcomes, prognostic factors and patterns of failure were analyzed. Results: After median follow-up of 62 months, there were 19 (35.2%) patients who had disease recurrence. Pure local failure within the PORT volume was found in 13 patients (24%) with either local (13.0%) or regional (10.4%) recurrence, and regional failure in adjacent mediastinum or lymph nodes in 3 (5.6%) patients with WHO type B3 or C TET. Overall survival rate at 5 and 10 years was 83.0% and 43.6%, respectively. Recurrence free survival rate at 5 and 10 years was 62.3% and 57.9%, respectively. The age ≤60 years old, female gender, and tumor diameter ≤1 cm were favorable prognostic factors for overall survival and univariate analyses. Radiation toxicity was mild in most patients and no severe toxicity was observed. Conclusion: PORT confined to the primary tumor bed only is suggested to be optimal in patients with Masaoka stage III (T1b-4N0) TET considering excellent in-field control and minimal out-field regional recurrences. Development of effective systemic treatment strategy to reduce the pleuro-pericardial seeding may be warranted.

Keywords: Patterns of failure, thymic epithelial tumor, Postoperative radiation therapy

P2.05-024 CURRENT STATUS OF STEREOTACTIC BODY RADIATION THERAPY (SBRT) IN JAPAN

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Background: Stereotactic body radiation therapy (SBRT) is a technique, introduced in the late 1990s. SBRT is a method of using single 10-20Gy of high dose and hypofractionated radiotherapy. Recently, many papers have been published on its clinical results, especially in early stage lung cancer. Methods: To recognize the current status of SBRT in Japan, a nation-wide survey was conducted by the Japan Conformal External Beam Radiotherapy Group (J-CERG). Results: The questionnaire was sent to 227 institutions. One-hundred and forty-nine institutions responded by the end of May 2015. The fixating apparatus, respiratory regulation, treatment planning and verification was surveyed. For regulation of respiratory movement, abdominal wall compression, breath-holding, respiratory gating and tumor chasing methods were used. For irradiation technique, 6 to 10-coplanar beams or multiple arc beams were mainly adopted. Conclusion: The current status of SBRT in Japan was recognized.

Keywords: SBRT, Radiotherapy
P2.05-025 9-YEAR EXPERIENCE: PROPHYLACTIC CRANIAL IRRADIATION IN EXTENSIVE DISEASE SMALL-CELL LUNG CANCER
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Background: In 2007, a EORTC study demonstrated a beneficial impact on overall survival with the use of prophylactic cranial irradiation in extensive disease small cell lung cancer. Nevertheless, there is ongoing debate over the role of PCI as patients in this trial did not undergo imaging of the brain prior to treatment, and a recent Japanese randomized trial showed a detrimental effect of PCI on OS in patients with a negative pre-treatment brain MRI. 87% of our patients received brain imaging prior to PCI. Methods: We examined the medical records of 137 patients with extensive disease small cell lung cancer who initially responded to chemotherapy and received PCI between 2007 and 2015. The outcomes, including the development of brain metastases and OS following PCI were analyzed. Survival and correlations were calculated using log-rank, univariate, and multivariate Cox proportional hazards-ratio analyses. Results: Median OS after PCI was 12 months and the median nPFS after PCI was 19 months. There was no significant survival difference in patients who received an MRI prior to PCI compared to patients who received PCI after PCI was 19 months. There was no significant survival difference in patients who initially responded to chemotherapy and received PCI between 2007 and 2014. Conclusion: Unfavorable prognostic factors for PORT were RT dose > 54 Gy, advanced T stage, poor Karnofsky performance status, advanced age, and left sided tumors. When irradiating left-sided tumors cardiac toxicity must be kept in mind.

Keywords: Re-irradiation, Brain metastasis, prophylactic cranial irradiation, SCLC; small cell lung cancer, st

P2.05-026 POSTOPERATIVE RADIOTHERAPY IN NON-SMALL CELL LUNG CANCER: 20 YEARS’ EXPERIENCE IN A SINGLE CENTRE
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Background: The purpose of this study is to evaluate the long term outcomes of postoperative radiotherapy (PORT) in patients with NSCLC. Methods: A total of 130 patients with resected NSCLC who were treated with PORT between January 1994 and December 2014 were respectively evaluated. Among the whole group 86 patients (66%) were treated with Co60 machines till 2005, and 44 patients (34%) with 6-10 MV photons with linear accelerators. Median RT dose was 54 Gy(range, 48-66 Gy) with 2 Gy daily fractions. The treatment fields covered the bronchial stump, ipsilateral hilum and mediastinum in 109 patients (83.8%), bronchial stump, ipsilateral hilum, mediastinum and supravacularvular nodes in 15 patients (11.5%); and bronchial stump and ipsilateral hilum in 4 patients (6.6%). Cisplatin-based chemotherapy was administered to 69 (53%) patients. Chemotherapy was applied preoperatively in 22 patients (17%), concomitantly in 27 patients (21%), and after PORT in 20 patients (15%). Overall (OA) survival, locoregional-free (LRF) survival and distant-metastasis free (DMF) survival were calculated using the Kaplan-Meier method. Results: The median age of the patients was 59 years (range 35-75 years). The most frequently performed surgical procedure was lobectomy (64.6%), followed by pneumonectomy (19.2%), wedge resection (10%), and bilobectomy (6.2%). Stages included I (19.2%), II (42.3%), IIIA (30.8%), and IIIB (6.9%). Neoadjuvant chemotherapy was applied to 62% of stage III patients. The median overall survival was 48 months. The 5-year OA, LRF and DMF survival rates for whole group were 43%, 75%, and 63% respectively. Significant prognostic factors for OA survival were indicated in the table. Conclusion: Unfavorable prognostic factors for PORT were RT dose > 54 Gy, advanced T stage, poor Karnofsky performance status, advanced age, and left sided tumors. When irradiating left-sided tumors cardiac toxicity must be kept in mind.

Keywords: postoperative radiotherapy, PORT, non-small cell lung cancer, radiation therapy

The Prognostic Factors for Overall Survival

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<td>KPS 70-80</td>
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<td>Dose &gt;4 54</td>
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Conclusion: Unfavorable prognostic factors for PORT were RT dose > 54 Gy, advanced T stage, poor Karnofsky performance status, advanced age, and left sided tumors. When irradiating left-sided tumors cardiac toxicity must be kept in mind.

Keywords: postoperative radiotherapy, PORT, non-small cell lung cancer, radiation therapy
POSTER SESSION 2 - P2.05: RADIOTHERAPY MULTIMODALITY TREATMENT – TUESDAY, DECEMBER 6, 2016

P2.05-027 EFFECTS OF THERMO-CHEMOTHERAPY FOR LUNG CANCER INDUCED BY NANO-PAACLITAXEL MAGNETIC FLUID
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Background: The aim of this study was to investigate the effects of thermo-chemotherapy induced by nano-paclitaxel magnetic fluid for lung cancer A549 proliferation, apoptosis and cell cycle in vitro, and therapeutic effect of single N2 station radiotherapy with PACLAN graft in nude mice in vivo. Methods: In vitro, nano-paclitaxel magnetic fluid was synthesised by chemical coprecipitation and ultrasound emulsification. Lung cancer A549 cells were set up the control group (group A), thermal therapy group (group B), chemotherapy group (group C) and thermo-chemotherapy group (group D), which exposed to an alternative magnetic field (AMF) for 30 min. And then the optical density (OD) of viable cell, cytotoxicity index, growth curve of cells, morphologic changes of cell, cell cycle and apoptosis were measured. When tumor length to diameter (6 - 8 mm), they were randomly divided into 4 groups: control group, magnetic heat treatment group, paclitaxel magnetic thermo-chemotherapy group and chemotherapy group, the tumor was heated in an AMF for 30 min. Tumor volumes were then measured every week. The therapeutic effect was assessed by measuring the tumor volume and weight. Pathological examination was performed with a light microscope following treatment. Immunohistochemical detecting tumor after treatment tumor cell apoptosis, calculate the apoptosis index to compare the efficacy of treatment. Results: In 43°C, with the increase of paclitaxel concentrations, are more obvious A549 lung cancer cell proliferation inhibition, the number of cells in living cells of optical density value, the killing rate (cytotoxicity index, CI). Cell apoptosis rate increased. Heat treatment group the stagnation of the cell cycle in 5 phase, 5 phase cells and G2 phase increases, 5 phase decreased in the chemotherapy group, after heat treatment of lung cancer cells in electron microscope magnetic apoptotic changes. The temperature inside the tumor can be quickly rise to 43°C. Tumors in three experimental groups are suppressed, magnetic thermo-chemotherapy group tumor growth inhibition is more obvious, immunohistochemical confirmed the tumor cell apoptosis in change, apoptosis index increased. Conclusion: In vitro, with the increase of paclitaxel concentrations, are more obvious A549 lung cancer cells proliferation inhibition in 43°C. The number of cells in living cells of optical density value, the killing rate (cytotoxicity index, CI), cell apoptosis rate increased. Thermo-chemotherapy induced by nano-paclitaxel magnetic fluid can inhibit the growth of A549 lung cancer nude mice transplantation tumor, nano paclitaxel magnetic thermo-chemotherapy can enhance the anti-tumor effect in vivo.

Keywords: Thermo-chemotherapy, magnetic fluid, chemotherapy, lung cancer

P2.05-028 COMPARISON OF ADJUVANT CHEMOTHERAPY WITH OR WITHOUT RADIOTHERAPY IN NSCLC PATIENTS WITH STAGE IIIA- SINGLE STATION N2
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Background: The role of adjuvant radiotherapy (ART) on stage IIIA-N2 NSCLC is still controversial especially in different status of lymph nodes invasion. We conducted this retrospective study here to evaluate the effect of adjuvant radiotherapy (ART) on non-small cell lung cancer (NSCLC) patients with resectable stage IIIA– single station N2. Methods: Between January 2010 and December 2013, 383 resectable NSCLC patients with stage IIIA-single station N2 were recruited in Shanghai Pulmonary Hospital. The patients received neoadjuvant therapy or no adjuvant chemotherapy (ACT) and were mixed with small cell lung cancer components were excluded from the study. Their clinicopathological data were collected and their survival times were recorded. The last follow-up was finished on May 31, 2016. Kaplan-Meier survival method was used here to calculate the overall survival (OS), disease-free survival (DFS) and Cox regression analysis was used to conduct multivariate analysis. Results: Overall 341 patients with median age of 59 yrs (25-79yrs) were included. There were 164 patients with adenocarcinoma (ADC), 106 with squamous cell lung cancer (SCC) and 61 others (37 with adenosquamous, 26 with large cell carcinoma and 8 with sarcomatoid carcinoma). Totally 26 patients were lost of follow-up. One hundred and eighty-nine patients (55.4%) were confirmed recurrence and 152 patients (44.6%) died until the last follow-up. Among them, 79 patients received ART and ACT after operation and 262 patients only completed ACT. The patients’ baseline characteristics of these two groups were balanced. The median DFS for the whole group patients, ART+ACT group and ACT group were 30 (23.9- 36.9) vs 31 (19.8-42.2) and 30 (21.3-34.2) months respectively. The median OS for the whole group patients, ART+ACT group and ACT group were 52 (39.4-66.4), 54 (NR) and 50 (36.7-63.3) months respectively. Multivariate analysis showed no difference in DFS and OS between ART+ACT and ACT groups. In subgroup analysis, we found the significant benefit in favor of ART (n=44) regarding DFS (HR 0.55, 95% CI 0.32-0.91, p=0.028) and no difference in OS (HR 0.553, 95% CI 0.284-1.078, p=0.082) in AD patients. While in SCC patients, ART (n=18) seemed a poor prognostic factor. (HR 2.0 for DFS, 95% CI 0.935-2.485, p = 0.074 and HR 0.757 for OS, 95% CI 0.225-2.553, p=0.654). Conclusion: ART significantly decreased the risk of recurrence in Adenocarcinoma patients with stage IIIA-single station N2 and might improve these patients’ survival. The benefit of ART for SCC patients didn’t be proved here.

Keywords: Adenocarcinoma, NSCLC, adjuvant radiotherapy, stage IIIA single station N2

POSTER SESSION 2 - P2.05: RADIOTHERAPY MULTIMODALITY TREATMENT – TUESDAY, DECEMBER 6, 2016

P2.05-029 MICROWAVE THERMAL THERAPY ENHANCES RADIOSENSITIVITY OF HIGHLY INVASIVE HUMAN NON-SMALL CELL LUNG CANCER H460 CELLS VIA INHIBITING DNA REPAIR
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Background: Hyperthermia has long been recognized as a modality in anticancer therapy. In present study, we provide an update on the recent knowledge about the molecular mechanisms of thermal radiosensitization on highly invasive NSCLC cells. Methods: In previous study, we isolated invasive subpopulations of cancer cells from established human non-small cell lung cancer (NSCLC) H460 cell lines. The subpopulation of highly invasive NSCLC cells (H460-INV) showed cancer cell stemness, increased DNA damage repair. H460-INV cells were exposed to hyperthermia and irradiation. Cell survival is determined by an in vitro clonogenic assay and growth curve for the cells treated with or without hyperthermia. Immunohistochemical staining assay was performed to detect the expression of Ki67 and γH2AX foci. Cell apoptosis was performed by Flow cytometry. Cell-scratches and transwell invasion chamber experiments were performed to detect the ability of cell migration and invasion. Western blot assay was used to detect DNA damage repair related molecular changes. Results: Hyperthermia can significantly enhance irradiation-killing cells. SER was 1.823. Ki67 and γH2AX fluorescence results suggested that thermo-radiation can significantly inhibit cell proliferation (p < 0.01). Flow cytometry results showed that the apoptotic cells increased significantly in heat treatment group (p < 0.05). Compared with the control group, H460-INV Cell migration and invasion ability significantly reduced. WB results suggested that thermal downregulated the expression of E cadherin, upregulated N-cadherin. Relative persistence of p-H2A.X nuclear foci in the H460-INV cells after RT treatment was observed, when compared to the no treat H460-INV cells. WB results suggested that thermal combined with radiation inhibited the DNA repair by inhibiting expression of Ku70 and Ku80. Conclusion: Microwave thermal therapy can increase the sensitivity of highly invasive NSCLC cells to radiation and its mechanism may be related to inhibition of radiation induced DNA damage repair, promoting tumor cell apoptosis, and thermo-radiotherapy can inhibit tumor cell invasion. This study suggests a beneficial clinical impact of microwave thermal therapy as a radiosensitizer for benefiting highly invasive lung cancer patients.

Keywords: hyperthermia, radiosensitivity, non small lung cancer, DNA damage repair

P2.05-030 WBRT PRIOR EGFR TKIS IS EFFECTIVE TREATMENT OPTION FOR NSCLC PATIENTS WITH CNS METASTASES HARBORING EGFR MUTATION
Pawel Krzyczkyć 1, Marcin Nicós 1, Dariusz Kowalski 2, Rodryg Ramiau 1, Kinga Wimarczyk 1, Katarzyna Szyksz-Bart 1, Katarzyna Reszka 1, Kamila Woda-
Abstracts

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P2.05-032 CT BASED SURROGATES OF PULMONARY VENTILATION IN LUNG CANCER: A VOXEL-LEVEL COMPARISON WITH HP GAS MRI

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Background: Image registration of paired inspiratory & expiratory CT is a potential method for generating surrogates of regional ventilation by assuming that local lung expansion & density changes of corresponding parenchymal voxels equate to ventilation. Potential lung cancer applications include functional lung avoidance radiotherapy planning and longitudinal assessment of treatment response. However, the physiological accuracy of the technique has yet to be validated. The aim of this study was to compare the spatial correlation of ventilation CT & He MRI in a cohort of lung cancer patients.

Methods: 5 patients underwent expiration & inspiration breath-hold CT with MRI. The median (range) Spearman's coefficient was 0.68 (0.45-0.76). Also mOS did not show significance discrepancies in both studied group.

Conclusion: This work demonstrates a method of acquiring CT & He MRI in a cohort of lung cancer patients.

Keywords: Pulmonary Function, non-small cell lung cancer (NSCLC), radiation treatment planning, radiation induced lung injury

POSTER SESSION 2 – P2.05: RADIOTHERAPY MULTIMODALITY TREATMENT – TUESDAY, DECEMBER 6, 2016

P2.05-031 THE CLINICAL IMPACT OF DIFFERENT CHEMOTHERAPY REGIMEN COMBINED WITH RADIOTHERAPY IN LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER

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Background: Different chemotherapy regimen have different toxicity for lung, which regimen can improve the therapeutic effect and reduce the toxicity reaction have not reached a consensus. This was a retrospective study to evaluate the clinical toxicity reaction and therapeutic of different chemotherapy regimen combined with radiotherapy for the treatment of locally advanced non-small cell lung cancer (NSCLC). Methods: 117 non-small cell lung cancer patients were randomly divided into 3 groups. (1) group A: the patients received concurrent chemotherapy consisting of gemcitabine/cisplatin combined with radiotherapy; (2) group B (the patients received concurrent chemotherapy consisting of paclitaxel/cisplatin combined with radiotherapy) and (3) group C (the patients received the concurrent chemotherapy consisting of Changchun vinorelbine, irinotecan, pemetrexed or other chemotherapy drugs/cisplatin combined with radiotherapy). All the patients received 2-4 cycles chemotherapy, and 2-2.2 Gy per fraction to a total of DT66-66 Gy thoracic radiotherapy 5 times per week. Results: The overall response rate (CR+PR) of the 3 group were: 37.5%, 24%, 20%(x2=4.909,p=0.037). In addition, the incidence of radiation esophagitis and bone marrow suppression in the three groups were 26.7%, 18.7%, 14.8 (P=0.832) and 26.7, 7.5, 0.0%, 33.3%, (P=0.024).

Conclusion: The patients received concurrent chemotherapy consisting of gemcitabine/cisplatin combined with radiotherapy could significantly increase the incidence of radiation pneumonitis, the patients received concurrent chemotherapy consisting of paclitaxel/cisplatin combined with radiotherapy had a high incidence of radiation pneumonitis. The local control rate and survival rate of the three groups were not statistically different.

Keywords: chemotherapy regime, non-small cell lung cancer, Radiotherapy

POSTER SESSION 2 – P2.05: RADIOTHERAPY MULTIMODALITY TREATMENT – TUESDAY, DECEMBER 6, 2016

P2.05-033 PREDICTORS OF SURVIVAL AFTER WHOLE BRAIN

Results: The mean registration error for the reference dataset was 1.1±0.2mm (mean±SD). Successful registration enabled computation of ventilation CT images at the inspiratory state and direct comparison of ventilation CT with MRI. The median (range) Spearman’s coefficient was 0.68 (0.45-0.76).

Conclusion: This work demonstrates a method of acquiring CT & He MRI in a cohort of lung cancer patients.

Keywords: Pulmonary Function, non-small-cell lung cancer (NSCLC), radiation therapy planning, radiation induced lung injury

POSTER SESSION 2 – P2.05: RADIOTHERAPY RT Techniques – TUESDAY, DECEMBER 6, 2016
Background: Whole Brain Radiotherapy (WBRT) has been the standard of care for multiple brain metastases, but due to its toxicity and lack of survival benefit, its use in the palliative setting has started to be questioned. New clinical algorithms regarding the correct use of WBRT are needed. Methods: This was a retrospective, single institution cohort study, consisting of 280 patients with brain metastasized Lung cancer who received WBRT at Karolinska University Hospital between 2010 and 2015. Information about RPA and GPA scores, demographics, histopathological results and received oncological therapy was collected. Predictors of Overall survival (OS) from the time of received WBRT were identified by Cox regression analyses. OS between GPA and RPA classes was compared by pairwise log rank test. A subgroup analysis was performed stratified by RPA class. Separate multivariate analyses were performed for RPA and GPA scoring systems, due to significant collinearity between them. Results: Median OS was 324, 130 and 41 days for RPA class 1(n=13), 2(n=165) and 3(n=101), respectively. Median OS for GPA groups 0 (0-1 points, n=168), 1 (1.5-2.5 points, n=98) and 2 (3-4 points, n=13) was 55, 166 and 110 days, respectively. Age>70 years was associated with worse OS. OS differed significantly between RPA class 1 versus 3 and 2 versus 3, GPA groups 0 versus 1 and age (p<0.0001 for all comparisons). Multivariate analyses are shown in table 1.

Conclusion: WBRT should be omitted for RPA class 3 patients. RPA class 1 patients should receive WBRT if clinically indicated. For RPA class 2 subgroup, patients with age>70 and GPA>1.5 points should be treated as RPA 3. WBRT is not considered in younger patients with GPA<1.5 points.

Keywords: RPA class, Brain metastasized Lung Cancer, Whole Brain Radiotherapy, GPA
After median of follow up of 33 months (10-45) we analyzed 27p, with median age of 74y (83-58), 21 males (78%). Main reasons for inoperability were: 7 (26%) poor respiratory function, 10 (37%) with multiple comorbidities and 6 (22%) who refused surgery. Location was RUL 9 (33%), RLL 6 (22%), LUL 7 (26%), LLL 4 (15%). Lung primaries in 19p (70%) and the main histologies were Squamous Carcinoma (7, 26%) and Adenocarcinoma (7, 26%). T1a (3, 11%), T1b (7, 26%), T2a (5, 18%) and T3 (7, 24%). Maximum grade of acute toxicity was GII (p=1.6), and for chronic toxicity was GII (aspiration) 4p (15%). Local Control at 30 months was 84% (three local failures, two from metastasis) and overall survival was 100% at this time. Conclusion: FFF beams using dose risk adapted schedule seem to be a safe approach with a good response profile. Further analysis with the entire cohort of the trial is needed in order to confirm these early results.

Keywords: SBRT, Lung, Trial

P.05-036 SINGLE FRACTION OF SBRT FOR PULMONARY LESIONS

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Background: Nowadays pulmonary oligometastatic disease it’s a common situation. SBRT for these patients is a feasible therapeutic choice. We present our experience using single fraction of 34Gy in solitary lesions in Lung. The main aim of this report is to show that single fraction of 34Gy in lung lesions is feasible, without toxicity and good response profile. Methods: 11 patients with 11 metastatic pulmonary lesions were prospectively treated with single dose of 34Gy. Inclusion criteria were: lesion size smaller than 2 cm, distance from the chest wall and main bronchus tree higher than 2 cm, in metastatic lesions primary tumour should be under control in PET scan. Patients were treated using True Beam machine (VARIAN). In 6 cases treatments were delivered without flattening filter beams. Median Age 68.7y (51-82), Gender distribution 3 women and 8 men. Histology: 4 cases (36.4%) were metastatic lesions from rectum, 2cases (18.2%) were metastatic lesions from Colon, 3 (27.3%) were primary lesions from lung, 1 (9.1%) was metastatic lesions from sigma and another 1 (9.1%) was from lachrimal gland. All patients underwent 4DCT for contouring. Immobilization was done by thermoplastic mask (Lorca sigma and another 1 (9.1%) was from lachrimal gland. All patients underwent 4DCT for contouring. Immobilization was done by thermoplastic mask (Lorca sigma) or stereotactic frame (Loma). Planning was done in inhomogeneous brain conditions. The planning target volume was defined by GTV with maximum diameter of 2cm. Results: Before November all patients were considered as CR to SBRT. However, at 48 weeks 2 patients were considered as non-CR. One of them was treated with True Beam and the other with True Beam SBRT. Conclusion: SBRT in solitary metastatic lesions is feasible, without toxicity and with good response profile. Further analysis is needed in order to confirm these results.

Keywords: SBRT, Lung, Single Dose
P2.05-039 ASSESSMENT OF LUNG TUMOUR MOTION COMPARING 4DCT, 4DCBCT AND MOTION OF IMPLANTED BEACONS DURING IMAGING AND IRRADIATION

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Background: Moving lung tumours exceeding the observed motion from planning 4D computed tomography (4DCT) can result in reduced dose coverage in stereotactic ablative body radiation therapy (SABR). 4D cone-beam CT (4DCBCT) facilitates verification of tumour trajectories before each treatment fraction. Using implanted Calypso beacons in the lung as ground truth, this work aims to assess how well 4DCT and 4DCBCT represent the actual motion range during imaging and irradiation. Methods: 4DCBCT was reconstructed for 1-2 fractions of 6 patients (three implanted Calypso beacons) receiving lung SABR from the projections acquired for treatment setup CBCT. Two reconstructions per projection set were created using the prior image constrained compressed sensing (PICCS) method based on the Calypso motion trajectories or an external respiratory signal (Philips Bellows). Calypso beacons were segmented for all 10 bins of the 4DCT and 4DCBCT sets and the centroid position calculated. Beacon centroid motion as seen on the 4DCT and 4DCBCT with respect to reference phase (end-exhale) was extracted and compared with the actual beacon centroid motion during CBCT acquisition and during irradiation. Results: Both methods for 4DCBCT reconstruction failed to capture sudden motion peaks during scanning (see Fig. 1), but performed similar to the 4DCT. In general, 4DCT and 4DCBCT underestimated the actual beacon centroid motion. In the SI direction 22-27% of the actual motion exceeded the motion range from 4D imaging. In AP and LR direction up to 39-58% of the motion exceeded the observed motion range from 4D imaging.

Conclusion: Both 4DCT and 4DCBCT failed to represent the full tumour motion range. For a safe treatment delivery this needs to be accounted for either by sufficient margins or more preferably real-time treatment adaptation directly tackling motion peaks and unpredictable motion.

Keywords: 4D computed tomography, 4D cone-beam computed tomography, real-time lung tumour motion, motion range comparison
P2.05-040 INTEROBSERVER VARIABILITY IN THE DEFINITION OF THE PRIMARY LUNG CANCER AND LYMPH NODES ON DIFFERENT 4DCT RECONSTRUCTIONS

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Background: Delineation variability is a major uncertainty in radiotherapy for lung cancer. As respiratory motion is an important part of this uncertainty, respiratory correlated computed tomography (4DCT) imaging is widely used. Several image reconstruction techniques are available to generate 3D data for delineation, such as the Maximum Intensity Projection (MIP) and the mid-ventilation (MidV) technique. The latter selects data at the time weighted mean tumour position. Both techniques are prone to motion artefacts. The new Mid-position (MidP) technique averages CT data after motion compensation to the mean position reducing such artefacts. The aim of this study is to evaluate interobserver variation for tumour delineation for these three image reconstruction techniques. Methods: 4DCTs of 10 patients were reconstructed using MIP, MidV and MidP methods. Seven specialised radiation oncologists delineated the primary tumour (GTVp) and lymph nodes (GTVln) on each reconstruction with a minimum of 4 weeks interval between delineations, using a provided protocol. The interobserver variation in the delineation of the GTVs was evaluated by calculating delineated volumes, conformity index (CI), and local SD between delineated contours (SDlocal) for GTVp and GTVln. Results: The differences in delineation variability are small (Table 1). The only significant differences are in overall volume (Friedman test); the MidP volume is slightly smaller than the MidV volume indicating a larger confidence in delineation. Counter-intuitively the observer variation was higher on the MidP images for the GTVln which seems to be related to increased reliance on the PET-CT images when delineating on the lower quality PET images.

Table 1: Interobserver variability in the delineation of the GTVp and GTVln

<table>
<thead>
<tr>
<th>Image</th>
<th>Mean Volume (cc)</th>
<th>Mean CI</th>
<th>Mean SDlocal (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GTVp</td>
<td>GTVln</td>
<td></td>
</tr>
<tr>
<td>MIP</td>
<td>81.91</td>
<td>0.568</td>
<td>0.363</td>
</tr>
<tr>
<td>MidV</td>
<td>66.17</td>
<td>0.576</td>
<td>0.327</td>
</tr>
<tr>
<td>MidP</td>
<td>62.23</td>
<td>0.602</td>
<td>0.337</td>
</tr>
</tbody>
</table>

Conclusion: Although not statistically significant, the MidP images had the highest CI, lowest volume and the lowest SD for the GTVp but not for the GTVln. Overall the MidP had the smallest interobserver variation. Adherence to delineation protocols for lymph nodes must be improved to benefit from the better image quality of MidP.

Keywords: Radiotherapy planning, Delineation variability, 4DCT reconstruction

P2.05-042 DEVELOPMENT OF THERAPEUTIC MAGNETIC RESONANCE IMAGING (MRI) FOR RADIOTHERAPY PLANNING

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Background: The ability to accurately visualize and delineate tumour and surrounding normal tissue is an essential component of radical radiotherapy treatment planning and in non-thoracic sites has been improved by integrating MRI. This early work investigated and optimized different MRI sequences for potential use in thoracic radiotherapy planning. Methods: 15 patients with primary lung cancer were scanned using a 1.5 Tesla scanner (Magnetom Aera; Siemens) and radiotherapy planning scanner (Philips Brilliance CT Big Bore, Philips Medical Systems). An identical patient immobilisation board was used (Extended Wing Board; Oncology Systems Limited) for both scans. Multiple MRI sequences were investigated and optimised to give similarity to contrast CT scans (3-4 mm slice thickness, whole thorax coverage and axial imaging). After reviewing the entire anatomic structure, ability to visualize the primary tumour, lungs, heart and oesophagus were scored using a 5-point system (1, unacceptable; 2, poor; 3, acceptable; 4, good; 5 excellent) and compared to CT (two tailed-t test).

Results: Respiratory triggered T2W SPACE (n=12) and T2W TSE (n=3) sequences suggest improved visualization of primary tumour (mean score 4.2 and 4.0) in comparison to CT (3.9, p<0.05). T2W TSE, T1W TSE (n=3) and T1W 2-point DIXON (n=5, breath hold) sequences may enhance oesophageal (4.3, 3.7 and 3.6) and cardiac (3.3, 4 and 3.4) visualisation, compared with CT (3.0, p<0.05). CT (n=15) was used as the optimal imaging modality for viewing lung nodules. The Cartesian VIBE (n=12, breath hold) provided no clear benefit over CT and diffusion-weighted single-shot-planar images (n=8) remain problematic due to image distortion.

Keywords: NSCLC, CHART, hypofractionated radiotherapy

P2.05-041 ACCELERATED RADICAL RADIOTHERAPY FOR NON SMALL CELL LUNG CANCER: SINGLE CENTRE EXPERIENCE OF TWO FRACTIONATIONS

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Background: Radical radiotherapy (RT) regimens for NSCLC vary considerably. In routine practice our centre has predominantly used continuous hyperfractionated accelerated radiotherapy (CHART, 54 Gy in 36 fractions over 12 days) and accelerated hypofractionated RT (55 Gy in 20 fractions over 4 weeks) since 1997. This report updates previous data presentation [1] including patients treated between 2005-2011. Methods: Case notes and radiotherapy records for all patients receiving radical radiotherapy were retrospectively reviewed. Patient demographics, tumour characteristics, RT and survival data were collected. Descriptive statistical analysis and Cox regression analysis was performed using SPSS. Results: 516 patients received radical radiotherapy, over 95% received CHART (237 patients) or hypofractionated RT (257). Median age was 70 yrs, and 60% percent were male. PET staging was performed in 81%, and 26%, 17% and 51% were stage 1, 2, 3 respectively. 81% were WHO performance status 0-1, 14% were squamous carcinomas, 21% non-squamous, 20% not otherwise specified, with 14% without histological diagnosis. Prior chemotheraphy was given to 36%, of whom 84% had stage III disease. 99.6% completed their prescribed radiotherapy treatment. 2 year survival was 47.5% and median overall survival from time of diagnosis was 23 months. Univariate analysis showed statistically significant association of survival with gender, stage and histology, but not age, PS or RT regime. Conclusion: Discussion: This single centre experience reflects the outcome of unselected consecutively treated NSCLC patients. Patient selection for the two radiotherapy regimens was largely down to patient preference for in- or out-patient treatment. Encouragingly, CHART outcomes seem a little better than those reported in the original CHART paper [2] and our previous cohort [1]. We feel this probably reflects improved patient selection following the introduction of PET staging into routine practice. Conclusions: The outcome for patients treated with accelerated radiotherapy fractionations in routine practice remains encouraging, and randomised trials comparing these approaches with conventionally fractionated chemoradiotherapy regimes are needed. 1. Pemberton LS, Din OS, Fisher PM, Hatton MQ. Accelerated radical radiotherapy for non-small cell lung cancer (NSCLC) using two common regimens: a single centre audit of outcome. Clinical Oncology 2009;21:161-7. 2. Saunders Met al. Continuous hyperfractionated accelerated radiotherapy (CHART) versus conventional cell lung cancer: a randomised multicentre trial. CHART Steering Committee. Lancet. 1997 Jul 19;350(9072):161-5

Keywords: NSCLC, CHART, hypofractionated radiotherapy
device was also mounted on the couch to get the external respiratory signal. To obtain 3D tumour trajectories, a Microsoft Kinect audio and depth sensing device was used. A Gold Anchor fiducial marker (0.4 mm diameter x 20 mm length) was implanted in the tumour near the right hilum (Fig 1, left). kV images were acquired at 5.5 Hz during VMAT. The fiducial marker was visible on 62.9% of the kV images. The average lung tumour motion (mean ± SD) in superior-inferior (SI), anterior-posterior (AP), and left-right (LR) directions were 0.27±7.52, -0.09±3.37, and -0.64±4.55 mm respectively. Seven fractions of lung tumour 3D motion and Kinect external signal were acquired, with the representative result illustrated (Fig 1, right). Conclusion: This is the first time that KIM has been used for intrafractional tumour motion monitoring during lung cancer radiotherapy, and also the first implementation of KIM on an Elekta imaging platform. This clinical translational research milestone paves the way for the broad implementation of image guidance to facilitate the detection and correction of geometric error for lung radiotherapy, and resultant improved clinical outcomes.

Keywords: kilovoltage intrafraction monitoring, tumour motion, Image guidance, Radiotherapy

**P2.05-043 LUNG TUMOUR MOTION KILOVOLTAGE INTRA FRACTION MONITORING (KIM): FIRST CLINICAL RESULTS**

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**Background:** Lung tumour positional uncertainty has been identified as a major issue that deteriorates the efficacy of radiotherapy. The recent development of the Kilovoltage intrafraction monitoring (KIM) which uses widely available gantry-mounted kilovoltage (kV) imager has been applied to prostate motion monitoring. This study reports the first clinical result of KIM for lung cancer radiotherapy with an Elekta machine. Methods: A locally advanced stage II lung cancer patient undergoing conventionally fractionated VMAT was enrolled in an ethics-approved study of KIM. A Gold Anchor fiducial marker (0.4 mm diameter x 20 mm length) was implanted in the tumour near the right hilum (Fig 1, left). kV images were acquired at 5.5 Hz during treatment. Post-treatment, markers were segmented and reconstructed to obtain 3D tumour trajectories. A Microsoft Kinect audio and depth sensing device was also mounted on the couch to get the external respiratory signal.

**Conclusion:** This preliminary study demonstrates the potential for MRI to improve the visualization of thoracic primary tumours, oesophagus and cardiac anatomy, all of which can be challenging to see on CT imaging, particularly in patients with collapse, consolidation or mediastinal tumour invasion.
experience on LC and OS. Results: Median follow-up time was 14.3 months (range 0-131.9 months) with 2-year LC and OS of 81.2% and 54.4%, respectively. In multivariate analysis, all treatment technologies except FG-PET staging did not significantly influence outcome. Patients who received pre-SBRT FG-PET staging showed superior 1- and 2-year OS of 82.7% and 64.8% compared to patients without FG-PET staging resulting in 1- and 2-year OS rates of 72.8% and 52.6%, respectively (p<0.012). SBRT treatment experience was identified as the main prognostic factor for local control: institutions with higher SBRT experience (patients treated with SBRT within the last 24 months) showed superior LC compared to less experienced centers (p=0.001). SBRT treatment experience within the last 24 months was independent from known prognostic factors for LC. Conclusion: Technological and methodical advancements except FG-PET staging prior to SBRT did not significantly improve outcome in SBRT for pulmonary metastases. On the contrary, LC was superior with increasing SBRT treatment experience of the individual center.

Keywords: stereotactic body radiotherapy, institutional experience, lung metastases, technological advancements

POSTER SESSION 2 - P2.05: RADIOTHERAPY
RT TECHNIQUES - TUESDAY, DECEMBER 6, 2016

P2.05-045 ACCELERATED RADICAL RADIOTHERAPY FOR NON SMALL CELL LUNG CANCER: SINGLE CENTRE EXPERIENCE OF TWO SCHEDULES IN THE TREATMENT OF ELDERLY PATIENTS

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Background: Radical radiotherapy (RT) regimens for NSCLC vary considerably and there is little data on outcomes for elderly patients, who are underrepresented in clinical trials. Our centre has routinely used continuous hyperfractionated accelerated radiotherapy (CHART, 54Gy in 36 fractions over 12 days) and accelerated hypofractionated RT (55 Gy in 20 fractions over 4 weeks) since 1997. We have examined outcomes for patients over the age of 80 treated between 2005 – 2011. Methods: Case notes and radiotherapy records for all patients receiving radical radiotherapy were retrospectively reviewed. Patient demographics, tumour characteristics, RT and survival data were collected. Descriptive statistical analysis and Cox regression analysis was performed using SSPS. Results: 516 patients received radical radiotherapy. 73 were over 80 years old, 71% were male, and 85% WHO performance status 0-1. PET staging was performed in 87%, with 4%, 22% and 32% being stage 1, 2, 3 respectively. 51% were squamous carcinomas, 18% non-squamous, 13% unspecified, and 19% without a confirmed histological diagnosis. 2 patients received primary chemotherapy. 40% received CHART, and 56% hypofractionated RT. All patients completed their prescribed radiotherapy treatment. 2 year survival was 67% and median overall survival from time of diagnosis was 22 months. Univariate analysis suggested stage was the only statistically significant variable associated with survival.

Conclusion: Our results confirm that accelerated radiotherapy schedules are deliverable in elderly populations with NSCLC who are generally not considered suitable for standard treatment with chemo-radiotherapy. The outcomes are similar to those reported in our younger patient cohorts [1] and appear to be as good as those reported in the original CHART paper [2]. Conclusions: The use of accelerated radiotherapy fractionations for the radical treatment of elderly patients with NSCLC is a feasible and well tolerated treatment for those patients not suitable for a chemo-radiotherapy approach. Outcomes are encouraging, but trials specific to this population are needed to define the optimal radiotherapy regimen. Ref: Pemberton LS, Din OS, Fisher PM, Hatton MQ. Accelerated radical radiotherapy for non-small cell lung cancer: a single centre audit of outcome. Clinical Oncology 2009; 21:161-7. 2. Saunders M et.al. Continuous hyperfractionated accelerated radiotherapy (CHART) versus conventional radiotherapy in non-small-cell lung cancer: a randomised multicentre trial. CHART Steering Committee. Lancet. 1997 Jul 19; 350(9072):161-5

POSTER SESSION 2 - P2.05: RADIOTHERAPY
RT TECHNIQUES - TUESDAY, DECEMBER 6, 2016

P2.05-046 IS Delineating CLINICAL TARGET VOLUME A MUST FOR MEDIUM AND LATE STAGES OF NON-SMALL CELL LUNG CANCER?

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Background: The main reason for a low progression-free survival rate in radiotherapy for NSCLC is that the lung is sensitive to radiation, and radiation-induced lung injury is closely related to the exposed volume of the lung tissues. A large irradiated volume will increase the risk of normal lung injury. If the lung tolerance is exceeded, the target dose, so clinically complete remission is very difficult in the primary lesion of the lung cancer. Therefore, as opinions are currently divided on whether it is necessary to delineate the CTV, this study aimed to study the impact of delineating CTV on the treatment of lung cancer. Methods: A total of 177 patients with medium and late stages of NSCLC diagnosed by pathology and/or cytology were selected. These patients received three-dimensional conformal radiotherapy (3-DCRT) or intensity modulated radiotherapy (IMRT) were divided into an undelineated CTV group (A group) and delineated CTV group (B group). Gross tumor volume (GTV) and planning target volume (PTV) were delineated in the A group, while CTV was additionally delineated in the B group. Dose was fractionated in pulmonary lesions in the two groups: 200-220Gy/time, 5 times per week, and the radiation dose was DT5600-6600Gy. The mean lung tumor doses were comparable between the two groups. Results: The short-term overall response rate had a trend to be higher in group B, while the 1-year, 2-year and 3-year distant metastasis rates, progression-free survival and overall survival rates had a trend to be higher in group A, but none of the differences were significant. The incidence of radiation pneumonitis was higher in group B (3.33% vs. 16.30%, P=0.017), but none were Grade 4 or worse. Conclusion: Undelineating the CTV in radiotherapy of lung tumors tends to reduce the radiation field and significantly reduce the incidence of radiation pneumonitis, but it doesn’t reduce overall response rate, the progression-free survival and overall survival rate.

Keywords: non-small cell lung cancer, radiotherapy, clinical target volume

POSTER SESSION 2 - P2.05: RADIOTHERAPY
RT TECHNIQUES - TUESDAY, DECEMBER 6, 2016

P2.05-047 FEASIBILITY STUDY: ASSESSMENT OF RT DOSE USING CARDIAC MRI CONTOURING METHODOLOGY ON RETROSPECTIVE LUNG PLANNING CT SCAN

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Background: Lung cancer related mortality remains high after radiotherapy (RT). Despite advances in treatment. The RTG0617 trial demonstrated increased mortality within the higher radiation dose treatment arm, though toxicity was similar between the two study arms. One possible explanation was, increased radiation dose to the heart. Typically radiation induced heart disease (RHD) is considered a late effect of RT in lymphoma and breast cancer. But RT dose prescribed in lung cancer is greater, and may result in acute effects in a population of patients with underlying cardio-pulmonary disease. Hence detailed dosimetric predictors are required for different cardiac morbidity endpoints. The CART study (2) was a prospective study investigating RHD with serial cardiac MRI scans and the team involved developed a technique to analyse radiotherapy dose to cardiac substructures without the MRI scan. Methods: CT planning scan was reformatted to develop a standardised method to outline in detail, cardiac substructures such as the left ventricular (LV) myocardium segments supplied by the coronary arteries (As). Other cardiac substructures such as cardiac chambers, conduction system and valves were contoured. This technique was applied to the planning scans of lung cancer patients and the dose to structures was calculated Results: Initially 5 patients who died within 3 months after RT were assessed. The RT treatment was 55Gy in 20 fractions over 4 weeks using 3D conformal RT technique. 3 patients had underlying cardiac or pulmonary comorbidities which were contoured as acceptance criteria for all patients to proceed with radical RT. Dose to OARs were acceptable and all patients completed treatment. Radiation dose to the heart – mean heart dose range 158Gy-1910Gy, maximum heart dose range 1521-5663Gy and V20 dose range 0%-36% and V50 dose ranged from 0%-19%. Dose to left ventricular myocardium – LAD territory was maximum dose range (MaxDR) 71-2086 (Gy) and mean dose range (MeanDR) 112-802 (Gy); LCX territory was MaxDR 71-2086 (Gy) and mean dose range (MeanDR) 112-802 (Gy); RCA territory was MaxDR 45-372 (Gy) and MeanDR was 44-178 (Gy) - demonstrated that anterior and lateral areas of LV myocardium received higher radiation doses. Dose to conduction system was high – SA node maximum dose range from 1140-5372 (cGy) and AV node maximum dose range was 103-1660 (Gy). Conclusion: It is feasible to use the CT planning scan to analyse retrospective patients for RT dose of coronary A myocardial territories, conduction system and other substructures. An analysis of a larger sample of patients is planned.
Keywords: CT planning scans, Cardiac toxicity, Radiotherapy, left ventricular dose

POSTER SESSION 2 – P2.05: RADIOTHERAPY TECHNIQUES – TUESDAY, DECEMBER 6, 2016

P2.05-048 DIRECTIONAL CHARACTERISTICS OF MOTION MARKER IN CBCT FOR TARGET LOCALIZATION FOR LUNG STEREOTACTIC BODY RADIOTHERAPY (SBRT)
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Background: Fiducial marker has been an effective and intuitive way to localize motion target for lung Stereotactic Body Radiotherapy (SBRT). However, due to the complexity for motion target imaging, the optimal target localization strategy still need to be developed to improve the efficiency and effectiveness of the clinical procedure. In this study, the golden marker moving in different directions was characterized in Conebeam CT images for optimal localization application. Methods: A Visicoil linear fiducial marker was selected for this study. The length and diameter of the marker were 5mm and 1mm. The motion was generated by Real Time Position Management (RPM) phantom from Varian Medical System. The motion was simulated to be about 2.3 seconds breathing period and about 1cm amplitude and phantom was positioned at three directions along the anterior-posterior (AP), left-right (LR), and In-Out (IO) of the couch. The CBCT images were taken in Truebeam On-board Imaging System. And targets were defined by auto-contouring with Hounsfield Unit (HU) setting from minus 900 to positive 4000 in Eclipse treatment planning system. The targets were post-processed with keeping the largest part, and converted to high resolution segment. Their characteristics were described by shape, volume, center of the volume and volume pixel information, which were attained by MIM Software. Results: In this CBCT study, for the given the contouring technique, the volumes of Viscoil fiducial marker were 0.286c, 0.35c, and 0.27c as moving along AP, IO and LR direction. They were corresponding to 14.3%, 16.3% and 23.6% of the static volume. The maximum HUs inside each moving target were 3395, 343 and 3097, which were 49%, 13% and 44% of those inside the static marker volumes. The center distances between the moving and static targets were 0.63cm in average with standard deviation at 0.02cm. Conclusion: When golden makers are applied for localization of treatment target in Lung SBRT, the geometric distance can be reflected in accurate level submillimeter; however, the directional motions could generate large HU difference, which is possibly a challenge to distinguish the boundary of moving tumor. And the directional motions could generate large HU difference, which is possibly a challenge to distinguish the boundary of moving tumor.

Keywords: Cone Beam Computer Tomography (CBCT), Image, fiducial marker, stereotactic body radiotherapy

POSTER SESSION 2 – P2.05: RADIOTHERAPY TOXICITIES – TUESDAY, DECEMBER 6, 2016

P2.05-049 RADICAL TREATED NSCLC RADIOTHERAPY PATIENTS: A PROSPECTIVE STUDY OF TOXICITIES AND OUTCOMES
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Background: Radical radiotherapy is widely used in the treatment of non-small cell lung cancer (NSCLC) among patients ineligible for surgery. Although side effects of radical radiotherapy have been well documented in clinical studies there is little real world prospective data describing their course, severity and effect on patient experience following treatment. Methods: NSCLC patients from the Beatson West of Scotland Cancer Centre (a specialised cancer care centre serving a population of 2.4m), treated with radical radiotherapy between September 2014 to December 2015, were offered followed up by a specialist nurse led clinic. This consisted of a telephone consultation at 2 weeks and clinic attendance at 2 and 6 months. Patient and tumour demographics were collected. Side effects were recorded at each visit and graded using the Common Terminology Criteria for Adverse Events (CTCAE). Descriptive statistical analysis was performed using Stata

Poster Session 2 - P2.05: Radiotherapy
Keywords: systemic inflammation, SBRT, sarcopenia

P2.05-050 IMPACT OF INFLAMMATION AND SARCOPENIA ON OUTCOMES AFTER STEREOTACTIC BODY RADIOTHERAPY FOR T1N0M0 NON- small cell lung cancer
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Background: The purpose was to evaluate impact of systemic inflammation and sarcopenia on outcomes after stereotactic body radiotherapy (SBRT) for T1N0M0 non-small cell lung cancer (NSCLC) as a supplementary analysis of Japan Clinical Oncology Group (JCOG) study JCGO403. Methods: Pretreatment serum C-reactive protein (CRP) was used as a marker for systemic inflammation. Patients were divided into high and low CRP groups with a threshold value of 0.3 mg/dL. Paraspinal musculature area (PMA) at a level of the 12th thoracic vertebra was measured on simulation CT with thresholding Hounsfield Units between -29 and 150. When PMA was lower than the gender-specific median, the patient was classified as sarcopenia. Toxicities, overall survival (OS) and cumulative incidence of cause-specific death were compared between groups: Kaplan-Meier method and cumulative incidence function were applied to estimate proportion of OS and cumulative incidence of cause-specific death, respectively. Results: Of 169 patients enrolled into JCGO403, 60 operable and 92 inoperable patients were included into this study after excluding 5 patients ineligible for JCGO403 and 12 patients whose simulation CT images were unavailable or unsuitable for the PMA measurement. Forty-two patients were classified as high CRP. Medians of PMA were 31.6 cm2 (range, 12.6-52.9) and 25.1 cm2 (range, 3.4-38.5) in male and female, respectively. Proportions of toxicities Grade 3-4 were 19.1% and 10.9% in the high and low CRP groups; and 17.1% and 9.2% in the sarcopenia and non-sarcopenia groups, respectively. In the operable patient cohort, OS significantly differed between the CRP groups (log-rank test P=0.009; hazard ratio of high CRP 2.43, 95% confidence interval 1.23-4.80; 3-year OS of 58.8% and 10.9% in the high and low CRP groups; and 17.1% and 9.2% in the sarcopenia and non-sarcopenia groups, respectively. In the operable patient cohort, OS significantly differed between the CRP groups (log-rank test P=0.092). No significant difference was observed in OS between the sarcopenia groups, either. Conclusion: The present study suggests that systemic inflammation may provide prognostic information for operable patients receiving SBRT for early-stage NSCLC. Further studies are warranted to confirm these findings.

Keywords: systemic inflammation, SBRT, sarcopenia

S557
P2.05-051 SAFETY OF LUNG STEREOTACTIC BODY RADIOTHERAPY (SBRT): A SINGLE INSTITUTION PROSPECTIVE STUDY BASED ON RTOG 0915 PROTOCOL CONSTRAINTS

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Background: To evaluate toxicity of RTOG 0915 protocol’s constraints in lung SBRT for patients treated with 60Gy in 5 fractions. Methods: Between 2010 and 2015, 77 pts were treated with SBRT for single or multiple lung lesions, 43 pts. (55.8%) for primary tumor and 34 pts. (44.2%) for metastatic lesion. A total of 80 lesions were treated. Four dimensional CT images were acquired, maximum intensity CT reconstruction was used for ITV delineation and average CT reconstruction for OAR contouring and dosimetric calculation. We prescribed 57Gy to 95% of PTV volume and OAR constraints are reported in table 1.

Table 1. SERIAL CONSTRAINTS

<table>
<thead>
<tr>
<th>Volume</th>
<th>Maximum Dose (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Card</td>
<td>10c</td>
</tr>
<tr>
<td>Trachea and large bronchus</td>
<td>40c</td>
</tr>
<tr>
<td>Brachial plexus</td>
<td>30c</td>
</tr>
<tr>
<td>Heart</td>
<td>150c</td>
</tr>
<tr>
<td>Large vessels</td>
<td>100c</td>
</tr>
<tr>
<td>Chest wall</td>
<td>70c</td>
</tr>
<tr>
<td>Esophagus</td>
<td>50c</td>
</tr>
<tr>
<td>Stomach</td>
<td>100c</td>
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</table>

Dose calculation was performed in 70% of the cases with collapsed cone convolution algorithm and 7 fields 3D technique and the remaining 30% with Monte Carlo dose calculation and intensity modulated fields (dynamic MLC and VMAT techniques). Treatments were delivered in 28% of the cases on Elekta-Precise accelerator with electronic portal films on-line setup verifications and the remaining 72% on Elekta-Agility accelerator with cone beam CT. We evaluated pre-treatment respiratory function and we treated only pts. with %FEV1 > 40%. We reported toxicity following CTCAE v3.0 score. Results: All the dose/constraints were respected except for the chest wall dose that was higher than 30 Gy in 8 pts. (10.3%). Toxicity was evaluated in all the patients except one that was lost in follow up. We found only lung or chest wall toxicity: 11 pts. (14.2%) with a G2 dyspnea, one patient with a G3 dyspnea; 8 pts. with a G2 chest wall pain and 1 with a symptomatic rib fracture.

We found more lung toxicity in patients with primary tumor because of more chronic lung disease prior to the treatment. Conclusion: The use of these SBRT constraints is safe in both metastatic and primary lung lesions, with a particular attention on pre-treatment respiratory function.

Keywords: SBRT, NSCLC, toxicity

P2.05-052 DISCUSSION AND ANALYSIS OF PNEUMONITIS RELATED TO STEREOTACTIC RADIOTHERAPY IN OUR HOSPITAL

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Background: Stereotactic radiotherapy (SRT) for lung tumors and related pneumonitis has been increasing, associated with the widespread use of SRT. However, insufficient research on pneumonitis related to SRT has been reported. Therefore, we attempted to clarify the clinical features and risk factors for pneumonitis. Methods: Between October 2011 and 2016, 91 patients received SRT for thoracic tumors in our hospital. We carried out a retrospective analysis of their data based on medical records and chest images, and we summarized the clinical features and the presence or absence of pneumonitis. Results: Of 91 patients who received SRT, 62 (68.3%) were men and 29 (31.7%) were women, with a median age of 77 years. Fifty-seven (62.6%) patients were smokers and 34 (37.4%) were non-smokers. Furthermore, 17 (18.7%) patients had pre-existing pulmonary fibrosis and 48 (52.7%) had pre-existing emphysema. The target diseases treated with SRT were 62 cases of primary lung cancer and 29 cases of other diseases (e.g., metastatic lung tumor). Pneumonitis related to SRT was observed in 74 cases (81.3%). Their grades (CTCAE version 4) were as follows: 54 (59.3%) cases of grade 1, 15 (16.5%) cases of grade 2, 4 (4.4%) cases of grade 3, 1 (1.1%) case of grade 4, and no cases of grade 5. Grade 2 or more severe pneumonitis was significantly higher in patients who had pre-existing fibrosis (p<0.016). Grade 3 or more severe pneumonitis, clinically serious, was observed in 5 cases (5.5%), of which 4 were men and 1 was a woman, and 4 were smokers. In addition, 4 of them had both pre-existing fibrosis and emphysema. All were treated with steroid therapy and improved. Conclusion: Pneumonitis related to SRT, including mild cases, was observed frequently. Pre-existing pulmonary fibrosis is suggested to be an independent risk factor for pneumonitis caused by SRT, as well as by conventional radiotherapy. However, even severe pneumonitis was improved by steroid therapy. These observations highlight the importance of steroid therapy. We will analyze more cases, including cases of pneumonitis in our hospital.

Keywords: Pneumonitis, Stereotactic ablative body radiotherapy

P2.05-052A SYSTEMATIC REVIEW AND META-ANALYSIS OF PNEUMONITIS IN RADIALLY TREATED NSCLC PATIENTS: SABR VS. NON-SABR TREATMENT

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Background: Purpose: SABR is popular because of the high rates of local control seen in lung cancer patients. However, prospective head to head trial data comparing the toxicity of SABR to conventionally fractionated radiotherapy are still awaited. We compare pneumonitis rates in SABR vs. non-SABR treatment for early stage lung cancer patients. Methods: Methods: A PUBMED search of all human, English language papers on SABR and non-SABR radically treated early stage lung cancer patients was performed until March 2016. The date range for the non-SABR patients extended back to January 1995, but the first 3D-CRT SABR papers assessed were found in 2003. Results of these searches were filtered in accordance to a set of eligibility criteria and analysed in accordance with the PRISMA Guidelines. Results: Results: The systematic search yielded a total of 184 SABR and 360 non-SABR articles, which were filtered down to 75 SABR and 23 non-SABR articles. SABR patients were older than non-SABR patients with 35/75 SABR papers and 67/23 non-SABR papers receiving a median age >75 years. Meta-analysis did not demonstrate a significant difference. We analyze pneumonitis rates in SABR vs. non-SABR patients receiving SABR [11.4% (95% CI of 9.7 to 13.3)] and non-SABR treatment [14.4% (95% CI of 10.6 to 18.8)]. Conclusion: Although meta-analysis did not confirm that SABR had lower rates of pneumonitis, it appears that SABR patients are older, and thus potentially more likely to have non-SABR radically treated patients. SABR is safe and has justifiably become the treatment of choice for inoperable patients.

Keywords: pneumonitis, Stereotactic ablative body radiotherapy

P2.05-054 RADIATION PNEUMONITIS: EARLY DIAGNOSIS AND PROTEIN EXPRESSION PROFILE IN NSCLC PATIENTS

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Background: Purpose: Pneumonitis is an adverse event that may occur after radiation therapy. We wanted to assess the protein expression profiles of NSCLC patients with radiation pneumonitis compared to NSCLC patients treated with radiation therapy but without pneumonitis. Methods: We performed a comprehensive literature search in MEDLINE and EMBASE. Remaining 85 papers after applying the exclusion criteria were used for the meta-analysis. Results: 41 NSCLC patients with radiation pneumonitis and 103 NSCLC patients without radiation pneumonitis were included. We found that the expression of several proteins was significantly different between these two groups. Conclusion: These differences may help to understand the mechanisms underlying radiation pneumonitis and to develop new therapeutic strategies.

Keywords: radiation pneumonitis, early diagnosis, protein expression profile, NSCLC patients
Background: Radiotherapy (RT) alone or in combination with chemotherapy (CT) are essential in treatment of non small cell lung cancer (NSCLC). A limitation for those therapies is the radiosensitivity of the lung. The aim of this study was to evaluate the incidence of radiation pneumonitis as well to identify potential markers for its early detection and to determine changes in the BAL protein expression. Methods: Fourteen NSCLC patients diagnosed at Multidisciplinary Lung Cancer Unit treated with chemotherapy-radiotherapy (CT-RT) or RT alone were enrolled in this prospective study. The collected variables were anthropometric values, lung function, tumor features and RT dosimetric data. A fiberoptichronoscopy for bronchoalveolar lavage (BAL) was performed in both lungs before RT and at the third week of treatment. The BAL protein expression profile was calculated from the last day of radiotherapy to the date of death. PFS was measured by cox proportional hazard model. The normality was determined with the Kolmogorov-Smirnov test. Student's t-test was used when variables had a normal distribution. Differences were considered statistically significant when p values were < 0.05. Results: All patients develop radiation pneumonitis, 35.75% of patients developed grade 1 pneumonitis, 20% grade 2, 35.75% grade 3 and 6.66% grade 5. Four patients developed pneumonitis in the lung without tumour. The decrease in lung diffusion capacity for carbon monoxide (DLCO) was the most sensitive parameter for determining the existence of early lung damage (p=0.04). Development of radiation pneumonitis was not associated with baseline lung function neither RT dosimetric data. The BAL protein expression profile was different between the two patients before RT. Expression of PAI-1, IL-1ra, MIF, and CXCL-1 in patient with pneumonitis grade 1 were increased only in the lung with tumor however these proteins were also increased in patient with pneumonitis grade 3 but in both lungs. It was significant that in the 2 cases RT induced similar changes in BAL protein expression in both lungs. Conclusion: In this prospective study, the incidence of radiation pneumonitis was greater than previously reported in the literature. The DLCO decline was the most sensitive parameter for its early detection. The risk to develop radiation pneumonitis appeared to be independent of dosimetric parameters and might be linked with the baseline inflammatory state. According to BAL protein expression analysis, RT produced comparable molecular changes in both lungs. Funded by SEPAR and IDIBELL.

Keywords: Lung cancer, radiation pneumonitis, lung function, protein expression

P2.05-056 SAFETY OF STEREOTACTIC BODY RADIOTHERAPY FOR CENTRAL, ULTRACENTRAL, AND PARAMEDIASTINAL LUNG TUMORS

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Background: Prior studies described increased toxicity following stereotactic body radiotherapy (SBRT) for central lung tumors. We report our institutional experience treating central lung tumors with SBRT, stratifying as central (C), ultracentral (UC) or paramediastinal (PM), and report toxicity for each cohort. Methods: The charts of all patients with centrally located lung tumors treated with SBRT Sept 2009 -June 2015 were reviewed. Eligible tumors were located within 2 cm of the proximal bronchial tree (PBT) or the planning target volume (PTV) overlapped the mediastium. Tumors were classified as UC if the PTV overlapped the PBT or esophagus, C if located within 2 cm of the PBT, and PM if abutting the mediastinum but not meeting criteria as C. Toxicity was scored with CTCAE v1.1. Results: We identified 42 patients treated to 46 centrally-located lung tumors (38 primary and 8 metastases) treated to a median dose of 50 Gy (range 40-60) over 3 fractions (range 4-8). Nine tumors (19.6%) were classified as UC, 29 (54.3%) as C, and 9 (18.6%) as PM. The median follow-up for living patients was 21.4 months (range: 11.5-63.5). Crude rates of grade 3+ toxicity for patients with UC, C, and PM tumors were 22.2%, 4.3%, and 0% respectively (p=0.11). Grade 3+ toxicity included 2 cases of grade 3 post-obstructive pneumonia and one case of grade 5 respiratory failure following SBRT for an UC tumor. PBT doses for UC tumors routinely exceeded standard constraints. Key dose volume metrics for each group are outlined in Table 1.

P2.05-057 BASELINE INFLAMMATORY AND IMMUNOLOGICAL PROFILE PREDICT THE SURVIVAL OF NSCLC PATIENTS UNDERGOING PALLIATIVE RADIOTHERAPY

Pierpaolo Pastina, Valerio Nardone, Paolo Tini, Giuseppe Battaglia, Stefania Croci, Cirino Bottai, Cristiano Pappalardo, Monica Ricci, Michele Caraglia, Antonio Giordano, Pierosandro Tagliabue, Tassone Pierfrancesco, Luigi Pirtoli, Pierpaolo Correale

P2.05-055 90 DAY MORTALITY AND SURVIVAL FOLLOWING RADICAL RADIOTHERAPY FOR NON-SMALL CELL LUNG CANCER TREATED IN THE DORSET CANCER CENTRE, UK

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Background: The prognosis from non-surgical treatment of non-small cell lung cancer remains poor. Patients are often elderly with multiple comorbidities. Evaluating toxicity and patient outcomes is essential to guide appropriate patient selection for intensive treatment. In addition to overall survival (OS) and progression free survival (PFS), 90 day mortality is increasingly recognised as a metric of service quality in the delivery of radiotherapy and reporting is recommended by the National cancer reform Strategy UK 2011. Methods: Consecutive patients were included who commenced radical radiotherapy between January 2013 and December 2015. 90 day mortality was calculated from the last day of radiotherapy to the date of death. PFS and OS were calculated from the last day of radiotherapy to the date of death. PFS was measured by cox proportional hazard model. Conclusion: In this study was to evaluate the incidence of radiation pneumonitis as well to identify potential markers for its early detection and to determine changes in the BAL protein expression. Patients who developed a recurrence were reviewed to determine if this was within the radiotherapy field. Results: 115 patients were included. The median age was 70 (range 63-96), recent trials such as RTTOG 9410 have an age limit of 75-79. Median follow-up was 14 months (range 1-38). The majority (61.7%) were stage II. 57.4% were ex-smokers, 41.7% were performance status 1 and 86% had a co-morbidity score of 1 or above (ACE27). 45.2% received radiotherapy alone, the remaining received concurrent chemo-radiotherapy . Patients (6%) died within 90 days. The 1 year PFS and OS were 70% and 81% respectively. Of the 49 recurrences, 26 (22.8%) were within the radiotherapy field. There was a correlation between a high V20 figure (volume of lung receiving 20Gy) and worsening survival (p=0.0218), measured by Cox proportional hazard model.

Maximum Point Dose in Gy: Median (range)

<table>
<thead>
<tr>
<th>Area</th>
<th>Central</th>
<th>Ultracentral</th>
<th>Paramediastinal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proximal Bronchial Tree</td>
<td>58.0 (46.5-57.9)</td>
<td>29.1 (21.5-51.2)</td>
<td>15.8 (2.3-28.6)</td>
</tr>
<tr>
<td>Esophagus</td>
<td>29.9 (11.1-41.2)</td>
<td>16.9 (4.3-37.9)</td>
<td>18.1 (9.7-33.2)</td>
</tr>
<tr>
<td>Heart</td>
<td>29.8 (5.2-37.8)</td>
<td>18.4 (0.3-62.4)</td>
<td>20.1 (1.4-61.1)</td>
</tr>
<tr>
<td>Great Vessels</td>
<td>59.7 (63.4-69.9)</td>
<td>41.1 (15.7-72.3)</td>
<td>51.9 (10.6-62.2)</td>
</tr>
</tbody>
</table>

Grade 3+ Toxicity n=2 (22.2%) n=1 (4.3%) n=0 (0%)

Conclusion: In our cohort, SBRT for UC tumors showed a trend toward increased high-grade toxicity, suggesting additional counseling regarding treatment risks for the subset of patients with UC lung tumors is warranted. Additional studies to optimize SBRT dose-fractionation schedules for patients with UC tumors are needed.

Keywords: Radiotherapy, SBRT, non-small cell lung cancer, toxicity
Background: Tie-2, VEGFA, VEGFC, VEGFR-1 and VEGFR-2 (angiogenesis), E-selectin, IL-1β, CA-IX and Osteopontin (hypoxia), Ang-1, Ang-2, FGFb, IL-8, PDGFb, PIGF, collected prior, during and post-radiotherapy and at the time of relapse. A comparison of the 4 time points revealed a much longer OS in those patients presenting serum levels of IL17 (p = 0.046), c-reactive protein (p = 0.056) and ESR nemo per estes (p = 0.014) lower than median value, after Mpe +/- bevacizumab and prior irradiation. We finally observed an increase in survival in patients showing a CD4+/CD8+ T cell ratio higher than median value (p = 0.050). Conclusion: These results suggest that palliative radiotherapy delivered after our metronomic regimen in mNSCLC is associated to a longer survival with a mechanism presumably driven by immunological effects. These results represent a solid rationale to test our metronomic regimen and RT in sequential combination with immune checkpoint inhibitors in mNSCLC patients.

Keywords: radiotherapy, chemo-immunotherapy, nsclc

POSTER SESSION 2 – P2.05: RADIOTherapy TOXICITIES - TUESDAY, DECEMBER 6, 2016

P2.05-058 BLOOD BIOMARKERS OF INFLAMMATION, TUMOUR BURDEN AND PROLIFERATION PREDICT RADIOTHERAPY RESPONSE AND TOXICITY IN LUNG CANCER

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Background: There is an unmet need to develop non-invasive biomarkers that can be used to tailor radiotherapy and select patients for future mechanism-based radiotherapy combination trials. The aim of this study was to assess blood biomarkers of radiotherapy response and toxicity in patients with lung cancer. Methods: This is a prospective exploratory study conducted at the Christie NHS Foundation Trust (Manchester, UK). Blood samples were collected prior, during and post-radiotherapy and at the time of relapse. A panel of 26 biomarkers were evaluated; M30 and M65 (apoptosis/cell death), CA-IX and Osteopontin (hypoxia), Ang-1, Ang-2, FGFb, IL-8, PDGFb, PIGF, Tie-2, VEGFA, VEGFC, VEGFR-1 and VEGFR-2 (angiogenesis), E-selectin, IL-1β, IL-6, IL-10, IL-12 and TNFα (inflammation), CYFRA 21-1, EGF, KGF and VCAM-1 (tumour burden, proliferation and invasion) and HGF (multiple processes). Clinical, demographic and treatment data as well as routine haematology and biochemistry test results were collected. Blood sampling and analysis were performed in a good clinical practice-compliant laboratory. Univariate analysis was performed on patients with small-cell and non-small-cell lung cancer (NSCLC) while multivariate analysis focused on patients with NSCLC. All statistical analyses were performed in R v3.1.1. Results: Between March 2010 and February 2012, blood samples from 78 patients were analysed. Forty eight (61.5%) were treated with sequential chemo-radiotherapy, 61 (78.2%) had stage IV disease (mNSCLC) while 35 (45.0%) had stage III disease. TNFα, IL-6, IL-8, IL-1β, KGF and IL-12 accounted for the bulk of the variability between patients at baseline. Of these, high TNFα (hazard ratio (HR); 2.27, 95% confidence interval (CI); 1.22-4.23, log-rank p = 0.008) and IL-1β (HR; 4.02, 95% CI; 2.04-7.93, log-rank p = 0.001) were the strongest covariates of survival. Of routinely-collected laboratory test results, neutrophil count was a significant covariate of survival (HR; 1.07, 95% CI; 1.02-1.11, log-rank p = 0.017). A multivariate survival prediction model for NSCLC was created by combining baseline IL-1β and neutrophil count. The addition of early-treatment (week 3) CYFRA 21-1 to this model modestly improved the survival prediction concordance probability (0.75; p = 0.029 to 0.78; p = 0.004). Chemotherapy was strongly correlated with acute oesophagitis (p = 0.001) while KGF was weekly correlated (p = 0.019). The addition of KGF did not improve a multivariate toxicity prediction model based on chemotherapy. None of the tested variables correlated with acute pneumonitis. Conclusion: Blood biomarkers of inflammation and proliferation and early-treatment tumour burden could provide additional information about radiotherapy response and toxicity in patients with lung cancer. Following independent validation, the proposed biomarkers could be integrated within future mechanism-based radiotherapy combination trials.

Keywords: Biomarkers, Radiotherapy, response, toxicity

POSTER SESSION 2 – P2.06: SCIENTIFIC CO-OPTERATION/ RESEARCH GROUPS

Phase I Trials – TUESDAY, DECEMBER 6, 2016

P2.06-001 A STUDY OF MGCD516, A RECEPTOR TYROSINE KINASE INHIBITOR, IN MOLLEULARLY SELECTED PATIENTS WITH NSCLC OR OTHER ADVANCED CANCERS

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Background: MGCD516 (Sitravatinib), is an oral, potent small molecule inhibitor of a closely related spectrum of RTKs including RET, the split RTKs (VEGFR, PDGFR and KIT), TRK family, DDR2, MET and AXL. RTKs inhibited by sitravatinib are genetically altered in NSCLC and other cancers, where they function as oncogenic drivers, promoting cancer development and progression. Alterations in these RTKs have also been implicated in tumor resistance mechanisms. Sitravatinib has demonstrated antitumor activity in nonclinical cancer models harboring genetic alterations of sitravatinib targets, including rearrangement of RET, NTRK, or CHRNA12 amplification. Phase I dose escalation has been completed, showing dose proportional increases in exposure. PK and preliminary PD data indicate inhibition of the targets at the 150 mg dose administered orally once per day. Methods: This phase 1b study involves enrollment of molecularly selected patients (pts) with unresectable or metastatic NSCLC or other advanced solid tumor malignancies in patient cohorts characterized by activating alterations in sitravatinib RTK targets (RET, KDR, PDGFR, KIT, TRK, DDR2, MET, AXL) or baseline evidence of function mutations in CBL, a negative regulator for MET, AXL, PDGFR and KIT signaling. Pts receive sitravatinib at 150 mg once daily in 21-day cycles. Study endpoints include safety and tolerability, PK/PD, and clinical activity assessed by objective disease response per RECIST 1.1, duration of response and survival. A two stage optimal Simon design of up to 24 pts in first stage and 16 pts in second stage was used. In addition, percentage of these cohorts defined by a specific tumor gene alteration assuming p0 =0.15 and m=2 was drawn to ensure sample size was not applicable

Keywords: Chromosome 4q21, Receptor Tyrosine Kinase Inhibitor, RET, CBL

S560

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IN JAPANESE SUBJECTS WITH ADVANCED SOLID TUMORS HARBORING EITHER A ROS1 OR NTRK FUSION GENE

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Background: Oncogenic gene fusions of ROS1 or NTRK have been reported in various cancers. DS-6051b is an orally available small molecule receptor tyrosine kinase inhibitor with high affinity for the ROS1 and NTRK receptors. Non-clinical pharmacology studies demonstrated antitumor activity of DS-6051b against several types of human tumor harboring ROS1 or NTRK fusion gene in cultured cells and xenograft models. Methods: This is an ongoing phase 1 study in Japanese subjects with advanced solid tumors harboring either a ROS1 or NTRK fusion gene. Subjects receive doses of DS-6051b from 400mg to 800mg once daily (QD). Pharmacokinetics (PK) samples are collected from Day 1 to Day 22. Primary objective is to assess the safety profile and secondary objectives are to determine the maximum tolerated dose (MTD), the recommended phase 2 dose (RP2D), and to assess the PK profile. The efficacy of DS-6051b is an exploratory assessment performed by investigator judgment per RECIST v.1.1. Results: As of June 27, 2016, a total of 9 subjects were enrolled. Median age was 51 (43-69) years, 56% were female, all 9 subjects were ROS1 fusion positive non-small cell lung cancer patients, and 3 subjects had prior crizotinib treatment. Subjects received DS-6051b at doses of 400mg QD (n=6) and 800mg QD (n=3). There were no DLTs in the 400mg QD cohort, and 2 out of 3 subjects in the 800mg QD cohort experienced DLT with grade 3 AST/ALT increased. To evaluate the MTD and RP2D more in detail, 600mg QD cohort is planned. Common adverse events were AST increased, ALT increased, diarrhea, and constipation. Among 7 patients who had target lesion, 4 subjects showed partial response, 3 subjects showed stable disease. PK data indicated the plasma drug concentration increases as the dose increases. Conclusion: This study is categorized as “Clinical Trial in Progress”. This study was initiated from February 2016 and estimated primary completion date will be September 2018.

Keywords: NSCLC, ROS1, Phase1, NTRK

P2.06-004 A PHASE IB STUDY OF THE COMBINATION OF AFAFINIB AND RUXOLITINIB IN EGFR MUTANT NON- SMALL CELL LUNG CANCER (NSCLC) PROGRESSED ON EGFR-TKI

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Devision of Medical Oncology, Department of Internal Medicine, Yonsei University College of Medicine, Seoul/Korea, Republic of

Background: In non-small cell lung cancer (NSCLC) patients treated with EGFR tyrosine kinase inhibitors (TKIs), acquired resistance is attributed to the T790M mutation in exon 20 in approximately 50% of cases. Despite promising preclinical findings, afafinib did not improve survival of patients with the T790M mutation. In a recent preclinical study, we demonstrated that autocrine IL-6 induced JAK/STAT3 signaling pathway mediated adaptive resistance to afafinib in H1975 and PC9-GR cells harboring T790M mutations. Knockdown of STAT3 with siRNA or pharmacologic JAK1 inhibition increased the anti-tumor activity of afafinib in T790M-positive NSCLC cells. Based on the promising preclinical results, we conducted a phase Ib study to evaluate the safety and efficacy of the combination of afafinib and ruxolitinib, a selective JAK inhibitor, in NSCLC patients who had progressed on EGFR-TKIs. Methods: For dose escalation with the classical 3+3 design, patients with histologically diagnosed, EGFR mutant stage IV NSCLC were considered eligible. Patients should have documented disease progression on EGFR-TKIs with clinical definition of acquired resistance. Afafinib was administered alone once daily from day 1 through day 8 (run-in period), then ruxolitinib was orally administered twice daily concomitantly with afafinib until progression. The primary endpoint was to determine RP2D and DLT.

Results: As of July 13, 2016, 15 patients (8 with exon19 deletion, 7 with exon21 L858R) were enrolled in the dose escalation cohort, 8 of which had T790M mutations. Patients were previously treated with erlotinib (n=5) or gefitinib (n=10). Patients received a median of 3 (range, 1-4) lines of chemotherapy. No DLT was observed at the highest dose level (afatinib 50 mg once daily plus ruxolitinib 25 mg twice daily). Frequent AEs included paronychia (G1 in 7 cases), diarrehea (G1 in 6 cases, G2 in 1 case), acneform rash (G1 in 5 cases), and oral mucositis (G1 in 1 case, G2 in 3 cases). SAEs were reported in 6 patients, which were not related to the investigational products. Partial responses were observed in 6 patients (40%) with disease control rate (CR+PR+SD) of 86.7%. Median PFS was 8.8 months (95% CI, 1.8-15.8) and 6 patients remain on study. Dose expansion with pharmacodynamic study at the RP2D will be open for NSCLC patients with EGFR T790M. Conclusion: The combination of afafinib with ruxolitinib was well tolerated and had promising clinical activity with durable disease control in NSCLC with acquired resistance to EGFR-TKIs (NCT02145637).

Keywords: Ruxolitinib, non-small cell lung cancer, EGFR-TKI resistance, afatinib
P2.06-005 PHASE I STUDY OF RAMUCIRUMBAN OR NECUTUMUMAB IN COMBINATION WITH OSIMERTINIB (AZD9291) IN ADVANCED T790M-POSITIVE EGFR-MUTANT NSCLC

David Planchard1, Mark Kris2, Benjamin Besse3, Rebecca Hozak4, Shuang He5, Frank van7, Katharina Wolff6, Bo Chao7, Helena Yu7
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Background: Despite the likelihood of an initial response to 1st or 2nd generation EGFR-TKI, EGFR mutants develop disease progression. The most frequent mechanism of acquired resistance is the EGFR T790M gatekeeper mutation. Novel treatment options are needed in this treated resistant patient population. Osimertinib, a third-generation EGFR TKI targeting mutant EGFR including T790M, is an oral, irreversible, selective inhibitor. Ramucirumab and necutumumab are human IgG1 monoclonal antibodies to VEGFR2 and EGFR, respectively. This phase 1, open-label, multicenter study with expansion cohorts (JVD/L; NCT02789345) is designed to evaluate the safety and preliminary efficacy of ramucirumab or necutumumab in combination with osimertinib in patients with advanced or metastatic EGFR T790M-positive NSCLC who have progressed after EGFR TKI therapy.

Methods: This study includes patients with advanced or metastatic EGFR T790M-positive EGFR activating mutant (exon 19 deletions or L858R) NSCLC, with measurable disease and ECOG performance status 0-1 who have experienced disease progression on one prior EGFR TKI regardless of prior chemotherapy. Patients previously treated with an EGFR antibody or 3rd generation EGFR TKI for NSCLC are not eligible. In the phase 1a dose-de-escalation portion (3+3 design), all patients (n=6 to 24) will be administered daily oral osimertinib (80 mg) with either an initial dose of 10 mg/kg IV ramucirumab or 600 mg IV necutumumab on days 1 and 8 of every 3-week cycle. One level of dose-de-escalation is planned for each arm. A dose reduction (level -1) to 8 mg/kg IV ramucirumab or 400 mg IV necutumumab is planned if 2 or more patients have DLTs in either arm. After the DLT evaluation, the study will open a dose-expansion portion (phase Ib) to 25 patients in each Arm, will receive study treatment until disease progression or a criterion for discontinuation is met. The primary objective is to assess safety and tolerability of ramucirumab or necutumumab in combination with osimertinib. Secondary endpoints include preliminary efficacy and pharmacokinetics. An exploratory biomarker objective includes the assessment of crosstalk between EGFR-mutant tumour tissue and serial blood samples with clinical outcomes. Primary analyses will be conducted approximately 6 months after the last patient receives initial dose. Results: Section not applicable. Conclusion: Section not applicable.

Keywords: osimertinib, ramucirumab, necutumumab, T790M
P2.06-008 PHASE 1/2 STUDY OF MOCETINOSTAT AND DURVALUMAB (MEDI4736) IN PATIENTS WITH ADVANCED SOLID TUMORS AND NON SMALL CELL LUNG CANCER (NSCLC)

Missak Haigenta1, John Nemunaitis2, Melissa Johnson1, Nisha Mohindra1, Keith Eaton, John Nemunaitis, Emanuel Pateli3, Mark Awad, Demiana Faltao4, Iscan Chen, Charles Berman1, Diane Potvin5, Tatjette Nessokri6, Edward Garon7

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Background: Immune checkpoint inhibitors produce durable clinical responses in a subset of patients, however strategies are needed to improve clinical efficacy of these agents and overcome innate or acquired resistance to therapy. Growing evidence suggests that tumors evade immune detection through modulation of intrinsic immunogenicity and inhibition of both innate and adaptive anti-tumor immune responses. Mocetinostat, a class I histone deacetylase inhibitor, has multiple potential immunomodulatory features including: 1) induction of tumor associated antigens and major histocompatibility complex Class I and Class II expression on tumor cells, 2) induction of immunogenic cell death via activation and cross-presentation of tumor antigens by antigen presenting cells, 3) enhanced function of T effector cells, and 4) decreased function of immunosuppressive cell subsets including regulatory T cells and myeloid derived suppressor cells. Given these pleiotropic immune affecting effects, combination therapy of mocetinostat and PD-L1 blocking mAb, durvalumab, is a rational approach to restoring or enhancing the clinical activity of immune checkpoint blockade in patients with NSCLC. Methods: This open-label Phase 1/2 study is evaluating the tolerability and clinical activity of mocetinostat in combination with durvalumab. Secondary objectives include: pharmacokinetics, immune checkpoint inhibitor and cancer mediator analysis, cytokines, biopsies, and changes in tumor PD-L1 expression. Exploratory objectives include changes in circulating and tumor cell PD-L1, circulating and tumor infiltrating immune cell populations and cytokines. Phase 1 explores increasing doses of mocetinostat administered orally (50, 70, 90 mg three times weekly [TIW]) in combination with durvalumab in patients with advanced solid tumors. The regimen begins with a 7-Day Lead-in Period of mocetinostat single agent TIW followed by the combination regimen with durvalumab (1500 mg intravenously every 28 days). Phase 2 evaluates the clinical activity of mocetinostat and durvalumab, as assessed by Objective Response Rate (ORR) by RECIST 1.1., in patients with NSCLC who have previously received at least one platinum containing doublet chemotherapy regimen for advanced disease. Four population cohorts are included: 1) immunotherapy naive, no/low PD-L1 expression, 2) immunotherapy naive, high PD-L1 expression, 3) prior clinical benefit with PD-L1/Or PD-L1 inhibitor treatment followed by progression, 4) prior treatment with PD-L1 or PD-L1 inhibitor with progression within 16 weeks of initiation of treatment. Tumor PD-L1 expression will be determined by the SP263 assay. The sample sizes for the populations are based on two-stage Simon Optimal Designs. Status: Enrollment into the study opened in June 2016. Clinical Trial Information: NCT02805660 Results: Section not applicable Conclusion: Section not applicable

Keywords: NSCLC, mocetinostat, durvalumab, MEDI4736

P2.06-010 AZD9291 AS 1ST-LINE THERAPY FOR EGFFR MUTANT NSCLC PATIENTS WITH CONCOMITANT PRETREATMENT EGF FR T790M MUTATION. THE AZENT STUDY

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Background: Osimertinib (AZD9291) is a selective and irreversible pyrimidine-based inhibitor of the primary activating and the secondary EGFFR mutation, T790M, which is the most common mechanism of acquired resistance to 1st and 2nd-generation EGF FR tyrosine-kinase inhibitors (TKIs). Progression-free survival (PFS) with osimertinib was 9.6 and 2.8 months (m) for EGFFR mutant (EGFFR+) NSCLC patients progressing to prior EGF FR TKI therapy with and without EGFFR T790M mutation, respectively, indicating that the T790M is a predictive biomarker for osimertinib efficacy. Sixty patients from two expansion cohorts of the same study, received 1st-line osimertinib and obtained a PFS of 19.3m. T790M, arising in cis with the primary activating mutation, confers resistance to EGF FR TKIs, even in the absence of drug selection. The coexistence of the pretreatment T790M mutation has been under appreciated, in spite of accumulative evidence that is present in a frequency of 35-60% using different detection methods. In our experience, pretreatment T790M mutation is frequently detected by three specific aspects of the method: tumor microdissection, examination of two separate tumor areas, and the use of a peptic nucleic acid clamp that inhibits wild-type allele amplification. Thus, we designed the first phase IIa study to evaluate the safety and efficacy of osimertinib as 1st-line therapy for patients with metastatic EGFFR+ NSCLC and concomitant pretreatment T790M mutation.

Methods: This is a multicenter, single-arm, open-label, non-controlled phase IIa clinical study in Spain. Eligible patients are aged ≥18 years with metastatic
EGFR+ NSCLC and by central testing documented presence of pretreatment T790M mutation. Seventy-three patients will receive continuous treatment with osimertinib 80 mg daily until disease progression, intolerable adverse events, consent withdrawal or noncompliance with the study protocol. The primary endpoint is the objective response rate (ORR) assessed using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. The trial is designed to detect a ≥70% ORR in this patient population. Secondary objectives include PFS, overall survival, time to treatment failure, duration of response and disease control rate. Additional pre-specified secondary objectives of the study are the longitudinal analysis of EGFR mutations (including the T790M and the C797S mutations) in plasma and serum and the expression analysis of a panel of biomarkers with possible predictive value for osimertinib treatment. Results: Not applicable Conclusion: Not applicable

Keywords: EGFR T790M mutation, AZENT study, ADZ9291, EGFR mutant NSCLC

P0.2.06-012 PHASE 2 STUDY OF ABEMACICLIB + PELBROZUMAB IN KRA S MUTATION, PD-L1+, STAGE IV NON-CELL-SMALL OR QUAMOUS CELL LUNG CANCER

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Background: Stage IV non-small cell lung cancer (NSCLC) harboring KRAS mutations remains a treatment challenge. Abemaciclib, a small molecular inhibitor of both cyclin-dependent kinase (CDK) 4 and 6, demonstrated acceptable safety, tolerability, and single-agent activity for patients with different tumors, including NSCLC. Preclinical evidence suggests a lethal interaction between CDK6 inhibition in lung cells and KRAS oncogenes. Pembrolizumab, a humanized monoclonal antibody against PD-1 protein, is approved in the US for patients with metastatic PD-L1+ NSCLC. Both compounds demonstrated manageable toxicities. We thus aim to study the combination of abemaciclib and pembrolizumab in pretreated patients with NSCLC. Methods: This open-label phase 2 study will evaluate safety and preliminary efficacy of abemaciclib 150 mg given orally every 12 hours on a continuous schedule on days 1-21 in combination with intravenous pembrolizumab 200 mg on day 1 of a 21-day cycle to patients in 1 of 3 disease cohorts: KRAS mutation, PD-L1+ stage IV NSCLC (Part A); stage IV NSCLC with squamous histology (Part B); or hormone receptor+, HER2- metastatic breast cancer (Part C). Total target accrual is approximately 75 patients (25 per cohort). Only the 2 NSCLC cohorts will be presented here. Patients eligible for Part A have a confirmed KRAS mutation, PD-L1+ expression score ≥29%, and are chemotherapy-naive for metastatic NSCLC. Part B includes patients with predominately squamous NSCLC who have received 1 prior platinum-based chemotherapy for advanced NSCLC. Patients must provide tumor tissue before and after treatment (cycle 3, day 1); have measurable disease, adequate organ function, an ECOG PS ≤1, and a life expectancy ≥6 months; and be able to agree to use no oral medications. The primary objectives are to characterize the safety profile of abemaciclib plus pembrolizumab. Secondary objectives include objective response rate (ORR), disease control rate (DCR), duration of response (DoR), progression-free survival (PFS), characterization of pharmacokinetics, and health outcomes. Patients who receive any study drug will be evaluated according to RECIST v.1.1 and irRECIST. Time-to-event variables will be estimated by Kaplan-Meier methodology. An interim analysis of safety and preliminary efficacy may occur after all patients have completed (or discontinued from) approximately 12 weeks of treatment. The final OS analysis will occur based on data collected for approximately 12 months after the last patient receives treatment. Results: Not applicable Conclusion: Section not applicable

Keywords: abemaciclib, pembrolizumab, non-small cell lung cancer, Squamous cell lung cancer

POSTER SESSION 2 – P0.6: SCIENTIFIC CO-OPERATION/RESEARCH GROUPS

P0.2.06-013 AFATINIB IN PATIENTS WITH ADVANCED HER2 MUTATION-POSITIVE (M+) NSCLC PREVIOUSLY TREATED WITH CHEMOTHERAPY

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Background: A retrospective analysis of 3 completed randomized Phase 2 studies of afatinib in patients with HER2+ NSCLC revealed a statistically significant benefit in overall survival (OS). The efficacy and safety of afatinib in patients with HER2+ NSCLC who have received previous chemotherapy treatment is not well understood. The primary objective of this study is to characterize the safety profile of afatinib in patients with HER2+ NSCLC who have previously been treated with chemotherapy. Secondary objectives include assessing the OS benefit of afatinib in this population.

Methods: The trial is a phase 3, open-label, randomized, multi-center study comparing afatinib vs. best supportive care (BSC) in patients with HER2+ NSCLC who have previously been treated with chemotherapy. Patients will be stratified by prior chemotherapy lines and will be randomized into a 2:1 ratio to receive afatinib or placebo. Secondary objectives include assessing the safety and tolerability of afatinib in these patients.

Results: Not applicable Conclusion: Not applicable

Keywords: afatinib, HER2+ NSCLC, previously treated with chemotherapy

POSTER SESSION 2 – P0.6: SCIENTIFIC CO-OPERATION/RESEARCH GROUPS
Background: Afatinib, an irreversible Erbb family blocker, inhibits signalling from all homo- and hetero-dimers of Erbb family members (EGFR [ErbB1], HER2 [ErbB2], ErbB3 and ErbB4). Based on the results of two large Phase III trials (LUX-Lung 3 [L3] and LUX-Lung 6), afatinib is approved in many countries for first-line treatment of patients with advanced EGFRm+ NSCLC. More recently, following results of the Phase III L8 trial, afatinib was also approved for treatment of squamous cell carcinoma of the lung after platinum-based chemotherapy. Overexpression/amplification of HER2 has been identified in NSCLC as a molecular mechanism of resistance to reversible EGFR tyrosine kinase inhibitors. Afatinib has demonstrated preclinical activity in HER2m+ lung cancer models and clinical activity in HER2m+ NSCLC patients (de Greve et al. Lung Cancer 2012; Mazieres et al. Ann Oncol 2015). This Phase II trial investigates the efficacy and safety of afatinib in patients with advanced NSCLC harboring HER2 mutations, previously treated with chemotherapy (NCT02597946). Methods: In this Phase II, open-label, single-arm trial, eligible patients are aged ≥18 years, with EGOG PS 0/1, histologically or cytologically confirmed stage IV NSCLC, confirmed HER2m+ tumour tissue, and measurable disease (RECIST v1.1), following failure of one or two prior chemotherapy regimens, of which one is platinum-based. Primary endpoint (except palliative treatment), chemotherapy or immunotherapy within 4 weeks, hormonal therapy within 2 weeks, or EGFR/HER2-targeted therapy is not allowed. In Part A of this two-part trial, patients will receive continuous oral afatinib monotherapy at the approved starting dose of 40 mg/day. The dose may be escalated to 50 mg/day after 4 weeks in patients with minimal drug-related adverse events (AEs); dose reduction by 10 mg decrements to a minimum of 20 mg/day will occur in case of drug-related grade 3 or selected grade 2 AEs. In Part B, patients with EGOG PS ≤2 experiencing ≥12 weeks of clinical benefit with afatinib monotherapy before disease progression will continue treatment with afatinib plus weekly intravenous paclitaxel 80 mg/m². In Parts A and B, treatment will continue until disease progression or intolerable AEs. The primary endpoint is objective response in Part A. Secondary endpoints include: disease control, progression-free survival, time to progression, and duration of response in Part A; and overall survival. Safety will also be assessed. Target enrolment is 40 patients, and participating countries will be listed in the full presentation. Results: Section not applicable. Conclusion: Section not applicable.

Keywords: NSCLC, afatinib, HER2, phase II

P2.06-015 THE NICE SALVAGE TREATMENT: A PHASE II TRIAL OF WEEKLY nab-PACLITAXEL IN THE SALVAGE SETTING FOR ADVANCED NON-SMALL CELL LUNG CANCER

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Abstracts

Background: The standard chemotherapy for advanced NSCLC after the failure of second or third line chemotherapy has yet to be established. In these salvage setting patients the acceptable safety and efficacy of solvent-based paclitaxel (sb-P) monotherapy have been previously reported as one possible treatment option (Anticancer Res 2005). Compared with sb-P, nab-paclitaxel(nab-P) yielded a higher mean maximal circulating concentration of free paclitaxel (280 vs 120 ng/mL for second line chemotherapy) and a favorable ORR in patients with advanced NSCLC (Lung Cancer 2016). However, there are no reports of nab-P monotherapy after the failing of second or third line chemotherapy. We therefore planned this study aiming to assess the efficacy and safety of nab-P monotherapy in patients with advanced NSCLC after the failure of second or third line chemotherapy.

Keywords: NSCLC, nab-paclitaxel, salvage, NICE

Objective Response Rate (ORR) by RECIST 1.1. Other objectives include safety, tolerability, pharmacokinomics and changes in circulating and tumor cell PD-L1, circulating and tumor infiltrating immune cell populations, cytokines and gene expression signatures. Enrollment into each Phase 2 treatment arm is stratified by prior outcome of CIT (e.g., clinical benefit versus progression of disease in ≤12 weeks). The investigational agents are administered orally in continuous regimens; nivolumab is administered intravenously, 3 mg/kg every 2 weeks. The sample sizes for the treatment arms are based on two-stage Simon Optimal Design. The US IND opened in June 2016. Results: Section not applicable. Conclusion: Section not applicable.

Keywords: Nivolumab, Immunotherapy resistant NSCLC, TAMS, tyrosine kinase inhibitor
POSTER SESSION 2 - P2.06: SCIENTIFIC CO-OPERATION/RESEARCH GROUPS
PHASE II - NK
TUESDAY, DECEMBER 6, 2016

P2.06-016 PHASE 2 STUDY OF RAMUCIRUMAB PLUS WEEKLY DOCETAXEL IN STAGE IV NSCLC FOLLOWING PROGRESSION AFTER PLATINUM-BASED CHEMOTHERAPY

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Background: Ramucirumab, a human IgG1 monoclonal antibody, binds to vascular endothelial growth factor (VEGF) receptor 2, competing with VEGF-A, C and D and thereby preventing receptor activation and angiogenesis. The phase 3 REVEL trial demonstrated the addition of ramucirumab to docetaxel improved survival in patients with stage IV NSCLC following progression after platinum-based chemotherapy, independent of histology. The approved dose of docetaxel in NSCLC patients after progression on prior platinum-based chemotherapy is 75 mg/m2 every 3 weeks. The most common toxicity associated with this dosing regimen is myelosuppression, specifically neutropenia. In order to reduce the incidence of myelosuppression, various weekly docetaxel dosing regimens have been evaluated. These studies have suggested that weekly docetaxel can provide better tolerability with at least similar efficacy. This phase 2, single arm, open-label study (JVDN; NCT02831491) is designed to assess a potential open-label study (JVDN; NCT02831491) is designed to assess a potential

Methods: Study JVDN includes patients (n=50) with stage IV NSCLC, with measurable disease and ECOG performance status 0-1 who have experienced disease progression on prior platinum-based chemotherapy for NSCLC. An exploratory endpoint is to assess the association between biomarkers with safety and clinical outcomes. The primary and final analyses will occur after 31 and 50 patients who did or did not receive prior immunotherapy. An exploratory endpoint is to assess the association between biomarkers with safety and clinical outcomes. The primary and final analyses will occur after 31 and 50 patients who did or did not receive prior immunotherapy.

Results: Not applicable. Conclusion: Not applicable.

Keywords: angiogenesis, VEGF, ramucirumab, docetaxel

POSTER SESSION 2 - P2.06: SCIENTIFIC CO-OPERATION/RESEARCH GROUPS
PHASE II - NK
TUESDAY, DECEMBER 6, 2016

P2.06-017 AMETHYST NSCLC TRIAL: PHASE 2 STUDY OF MGD265 IN PATIENTS WITH ADVANCED NSCLC WITH ACTIVATING GENETIC ALTERATIONS IN MET

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Background: MGD265 is a potent, orally available, small molecule RTK inhibitor of MET and Axl, both of which mediate signals for cell growth, survival, and migration. The AMETHYST NSCLC trial is designed to evaluate the activity of MGD265 in patients with NSCLC exhibiting genetic alterations involving MET. Alterations in MET, including gene amplification and/or genetic mutations, occur in approximately 7% of NSCLC cases converting MET to an oncogene capable of driving cancer development and progression. Amplification of MET has been associated with a poor prognosis in NSCLC. In addition, various genetic mutations in the deletion of exon 14 in MET mRNA (METex14del) and the subsequent loss of the Y1003 regulatory binding site for CBL ubiquitin ligase, required for MET degradation and signal attenuation. Loss of the Y1003 binding site of MET results in sustained MET signaling, which has been implicated as an oncogenic driver of a subset of NSCLC. The importance of MET as a driver is demonstrated in xenograft models of NSCLC with METex14del and MET amplification, and where MGD265 induces tumor regression. Additionally, confirmed partial responses have been observed in pts with NSCLC characterized by METex14del who were treated with MGD265 in the Phase 1 setting. In this Phase 2 trial, pts with platinum pre-treated NSCLC characterized by activating genetic MET alterations identified in tumor tissue or circulating tumor DNA (ctDNA) are eligible for this multi-center, global, Phase 2 trial. Pts are assigned to one of four cohorts based on the type of MET dysregulation and detection method: 1) mutations in tissue, 2) amplification in tissue, 3) mutations in ctDNA, and 4) amplification in ctDNA. The primary endpoint is Objective Response Rate (ORR) in accordance with RECIST 1.1, a Bayesian Predictive Probability Design is applied independently to each cohort. Secondary objectives include safety, tolerability, response duration, survival, correlation between tissue and ctDNA testing, and PK/PD. This study is currently open globally, and recruitment is ongoing. Results: Section not applicable. Conclusion: Section not applicable.

Keywords: MET, NSCLC, ctDNA, EXON 14 DELETION

P2.06-018 MULTICENTER, SINGLE-ARM PHASE II STUDY OF NAB-PACTAXEL/CARBOPlatin IN UNTREATED PS2 PATIENTS WITH ADVANCED NSCLC: TORG1426

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Background: No standard of care exists for ECOG Performance Status (PS) 2 patients with advanced non-small cell lung cancer (NSCLC) and therefore clinical practice ranges from supportive care to combination chemotherapy. It was first reported that the combination therapy with carboplatin (CBDCA)/pemetrexed significantly improved survival for PS2 patients with advanced non-squamous NSCLC (J Clin Oncol 31:2849-2853.2013). However, due to the limited utilities of this regimen, establishment of other combination therapy is warranted in PS2 patients with especially squamous NSCLC or unfavorable renal function. On the other hand, in CA03 trial, CBDOCA/nab-pacliaxel (PTX) demonstrated a significantly higher response rate (RR) compared with...
CBDCA/PTX in PS0-1 patients with advanced NSCLC, especially squamous histology, has shown clinical benefit compared to chemotherapy. Atezolizumab therapy improved overall survival compared to chemotherapy in randomized clinical trials. Atezolizumab is a humanized IgG1 monoclonal PD-L1 antibody that inhibits the interaction of PD-L1 with its receptor PD-1 on immune cells. Methods: Trial design: This phase II, open-label, single-arm trial randomized 2:1 to the treatment group (Genexol-PM+ cisplatin) and the control group (paclitaxel+ cisplatin). Patients were treated with Genexol-PM 230mg/m² intravenously without premedication or paclitaxel 175mg/m² intravenously with premedication plus cisplatin 70mg/m² on day 1 of a 3-week cycle for up to 6 cycles. Intrapatient dose escalation of Genexol-PM to 300mg/m² was carried out in treatment group from the second cycle if the objective response was achieved.

Background: Genexol-PM is a novel Cremophor EL(CrEL)-free polymeric micelle formulation of paclitaxel. This multicentre study was designed to compare Genexol-PM and CrEL-based paclitaxel in combination with cisplatin in terms of efficacy and safety as first-line therapy in advanced non-small cell lung cancer. Methods: Chemonaive patients aged from 18 to 70 years with histologically or cytologically confirmed, locally advanced, metastatic or recurrent advanced NSCLC and an ECOG performance status of 0–1 were randomised 2:1 to the treatment group (Genexol-PM+ cisplatin) and the control group (paclitaxel+ cisplatin). Patients were treated with Genexol-PM 230mg/m² intravenously without premedication or paclitaxel 175mg/m² intravenously with premedication plus cisplatin 70mg/m² on day 1 of a 3-week cycle for up to 6 cycles. Intrapatient dose escalation of Genexol-PM to 300mg/m² was carried out in treatment group from the second cycle if the objective response was achieved.

Results: Section not applicable Conclusion: Section not applicable Keywords: non-small cell lung cancer, Genexol-PM, paclitaxel
1 and Phase 2 trials in the US, Japan, Taiwan, and Korea have demonstrated antitumor activity and overall tolerability of ASP2783 at doses of 100mg–300mg. Methods: This global, multicenter, open-label, randomized, Phase 3 study will enroll ~600 subjects with Stage IIIb/IV NSCLC with EGFR activating mutations (ex19del or L858R, with or without T790M) who have not been treated with an EGFR inhibitor TKI (NCT02588261). Subjects will be randomized 1:1 to treatment with either 300mg oral ASP2783 QD or erlotinib/gefitinib. Each subject will receive a comparator drug (150mg erlotinib QD or 250mg gefitinib QD) at the beginning of the study. Randomization will be stratified by EGFR status (0, 1, or 2), EGFR mutation (ex19del, L858R), comparator selected (erlotinib vs gefitinib), and race (Asian vs non-Asian). Subjects will not be enrolled if they harbor both ex19del and L858R. All subjects will begin treatment on Day 1 Cycle 1 and will continue on 28-day continuous dosing cycles until the subject discontinues (eg, due to radiologic progression as determined by RECIST or unacceptable toxicity). Dose reductions will be allowed for ASP2783 and erlotinib, but not for gefitinib. The primary study objective is PFS as assessed by independent radiological review (IRR); secondary study objectives are overall survival, best overall response rate, duration of response and proportion of platinum-based chemotherapy. The primary endpoint is overall survival, of the study treatment, described below, over gefitinib monotherapy. As the study treatment, gefitinib are administered on days 1-56. Then, after a two-week drug-free period, three cycles of cisplatin and pemetrexed with gefitinib for 12 months. Results: Not-applicable Conclusion: Not-applicable

Keywords: MED14736, tremelimumab, duvalumab, Checkpoint blockade

P2.06-023 A PHASE III STUDY COMPARING GEFITINIB AND INSERTED CISPLATIN PLUS Pemetrexed with Gefitinib for EGFR-MUTATED ADVANCED NON-SQUAMOUS NSCLC

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Background: Combining platinum-doublet chemotherapy with EGFR-TKIs might prevent the emergence of acquired resistance to EGFR-TKIs and prolong the patient survival. An early phase II study of inserted cisplatin and docetaxel with gefitinib showed promising outcomes, including a median progression-free survival of 19.3 months and median survival time of 48.0 months. Methods: This study (JCOG1404/WJOG8214L, AGAIN study) is a single-arm, multicenter, randomized phase III study conducted by the Japan Clinical Oncology Group (JCOG) and the West Japan Oncology Group (WJOG). The objective of this study is to confirm the superiority, in terms of the overall survival, of the study treatment, described below, over gefitinib monotherapy. As the study treatment, gefitinib is administered on days 1-56. Then, after a two-week drug-free period, three cycles of cisplatin and pemetrexed are administered on days 71, 92, and 113. Thereafter, gefitinib is
re-started on day 134 and continued until disease progression. The secondary endpoints are progression-free survival, response rate, adverse events, severe adverse events and proportion of EGFR T790M mutation positive in the tumor samples at disease progression. The key eligibility criteria are: patients with advanced or recurrent non-squamous NSCLC harboring EGFR activating mutations (exon 19 deletion or exon21 L858R), age 20 to 74 years, and PS 0 or 1. This study was started in December 2015, and a total of 500 patients will be enrolled over a period of 3 years. This trial has been registered at UMIN-CTR (umicr.jp/ct03) as UMIN000020242. Results: Section not applicable

Conclusion: Section not applicable

Keywords: platinum-doublet chemotherapy, non-small cell lung cancer, EGFR mutation, gefitinib

POSTER SESSION 2 – P2.06: SCIENTIFIC CO-OPERATION/RESEARCH GROUPS
PHASE III – TUESDAY, DECEMBER 6, 2016

P2.06-024 TEOPOVI VS STANDARD TREATMENT AS 2ND OR 3RD LINE IN HLA-A2 POSITIVE ADVANCED NSCLC PATIENTS IN A PHASE 3, RANDOMIZED TRIAL: ATALANTE-1
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Background: HLA-A2 is expressed in 40 to 50% of NSCLC patients. TEOPOVI is a combination of neoptetopes that generates cytotoxic T lymphocytes responses. It consists of nine HLA-A2 supertype binding epitopes covering five tumor-associated antigens overexpressed in advanced NSCLC and the universal helper pan-DR epitope. In a phase II trial (NCT00104780, Barve et al, JCO 2008), TEOPOVI showed a promising median overall survival of 17.3 months with a manageable safety profile in pre-treated HLA-A2 positive patients with advanced NSCLC. ATALANTE-1 (NCT02654587) is a randomized, open-label, phase 3 study comparing the efficacy and safety of TEOPOVI with standard treatment in HLA-A2 positive patients with advanced NSCLC, as second- or third-line therapy. Methods: Section not applicable Results: Trial design: Patients with advanced NSCLC without EGFR-sensitizing mutations or ALK rearrangements, with progressive disease to first-line platinum-based chemotherapy or second-line immune checkpoint inhibitors (IC) are eligible if they have HLA A2 positivity and ECOG PS 0-1. Treated and asymptomatic brain metastases are allowed. Patients are randomized 1:1 to receive 1 ml TEOPOVI subcutaneously Q3W for 6 cycles, then every two months for the remainder of the year and finally every three months or standard treatment with bevacizumab 15 mg/kg and etoposide 100 mg/m2 (in non-squamous histology and pemetrexed-naive patients). In both arms, treatment continues until progression, intolerable toxicity, consent withdrawal, or investigator decision. In TEOPOVI arm, treatment may continue beyond initial randomization until disease progression in case of clinical benefit. Randomization is stratified by histology (squamous vs. non-squamous), initial response to first-line chemotherapy (partial or complete response vs. stabilization or progression), and previous treatment with IC (yes vs. no). Tumor assessment is performed every 6 weeks and adverse events are collected throughout the study and for 90 days after the last dose. 3-year survival rate is the primary endpoint. Archival biopsies samples are required for assessing PD-L1 status (H22C2 pharmDx from Dako). Primary endpoint is overall survival; and secondary are progression free survival based on RECIST 1.1 criteria, objective response rate, disease control rate, duration of response, and quality of life measured by EORTC QLQ C30. Second endpoint is a superiority study with the hazard ratio of 0.739, two-sided alpha 5% and power 80%, after 356 events are observed over 500 patients. The first patient was enrolled on 25th January 2016. Enrolment is ongoing in Europe and the US. Clinical trial identification: NCT02654587

Legal entity responsible for the study & Funding: OSE Immunotherapeutics, France Conclusion: Section not applicable

Keywords: non-small cell lung cancer, Second-line, HLA-A2, TEOPOVI

P2.06-025 DREAM - A PHASE 2 TRIAL OF DURVALUMAB WITH FIRST LINE CHEMOTHERAPY IN MESOTHELIOMA WITH A SAFETY RUN IN ANGIO-INOSE, P. P., Peey-Sei Koh, Ann Livingstone, Willem Joost Lesteherus, S. Yagi, Mark Donegan, Wei-Sen Lam, Martin Stockler

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Background: Immunotherapy is active in malignant pleural mesothelioma (MPM). Durvalumab is a human monoclonal antibody directed against the programmed cell death ligand 1 (PD-L1). The objective tumour response rate using modified RECIST for MPM and modified immune-related response criteria; adverse events and overall survival. Tertiary correlative objectives include associations between potential predictive/prognostic biomarkers and clinical outcomes. TREATMENT: Durvalumab 1125mg (dose to be confirmed in safety run-in), cisplatin (75mg/m2) and pemetrexed (500mg/m2) 3-weekly for a maximum of 6 cycles, followed by durvalumab alone until progression or for a maximum of an addition of 12 cycles. STATISTICS: 6 participants in an initial safety run-in using a 3+3 design, will be included in the total sample size of 54 evaluable participants, consisting of 31 recruited in stage 1, and another 23 in stage 2. The null hypothesis is that the true PFS rate is 45%, in keeping with standard therapy and would be considered not worthy of further evaluation. The two-stage design provides greater than 90% power with a one-sided type I error rate of 5% if the true PFS rate is 65% (alternate hypothesis). ASSESSMENT: CT scans weekly for the first 30 weeks, then 5-weekly until disease progression. Translational research blood collections: baseline, cycle 2 and 3. Results: Central ethics submission has been completed and recruitment will be updated. Conclusion: DREAM is an investigator-initiated cooperative-group trial led by ALTG, in collaboration with NHMRC Clinical Trials Centre, University of Sydney, with support from Astra-Zeneca

POSTER SESSION 2 – P2.06: SCIENTIFIC CO-OPERATION/RESEARCH GROUPS
MESOTHELIOMA AND SCLC - TUESDAY, DECEMBER 6, 2016

P2.06-026 A PHASE II TRIAL OF THE ORAL FGFR INHIBITOR AZD4547 AS 2ND OR 3RD LINE THERAPY IN MALIGNANT Pleural Mesothelioma – Trial in Progress
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Background: Dysregulation of the fibroblast growth factor (FGF) pathway is observed in a variety of cancers, including mesothelioma. FGF-9 is significantly over-expressed in mesothelioma and our pre-clinical data demonstrates that inhibition of FGF receptor (FGFR)-mediated signalling in vitro results in anti-proliferative and pro-apoptotic activity. FGFR targeted tyrosine kinase inhibitors strikingly reduce tumour burden in three separate murine models of mesothelioma. AZD4547 is a potent and selective oral FGFR 1,2 and 3 tyrosine kinase inhibitor that inhibits FGFR-related signal transduction pathways which makes AZD4547 appropriate to test in MPM in the context of strong preclinical rationale. Common side effects include dry mouth, mucositis and decreased appetite. Serious side effects include ophthalmologic toxicity, such as Retinal Pigmented Epithelium Detachment (RPED), conjunctivitis and corneal atrophy, hyperphosphatemia leading to cardiac mineralisation and renal failure. Methods: The study is an open-label single centre phase II trial of single-agent oral AZD4547 in patients with confirmed, measurable MPM who have progressed after 1st or 2nd line chemotherapy. Key inclusion/exclusion criteria include ECOG performance status 0-1, adequate organ function, and drug-specific ophthalmologic and cardiac exclusion criteria. The primary endpoint is 6 month progression-free survival (PFS-6), with secondary end points of objective tumour response (modified RECIST), PFS, overall survival, toxicity and treatment duration. We will enrol 26 patients in the first 2
Abstracts

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P2.06-027 RANDOMIZED PHASE II STUDY OF ANETUMAB RAVTANSINE OR VINORELBINE IN PATIENTS WITH METASTATIC PLEURAL MESOTHELIOMA AND SCLC –

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Background: Mesothelioma is a rare but aggressive cancer with a poor prognosis. Mesothelin is a cell surface protein that is highly expressed in mesothelioma and other epithelial cancers. Anetumab ravtansine (BAY 96-9343), a novel fully human anti-mesothelin IgG1 antibody conjugated to the maytansinoid tubulin inhibitor DM4, has shown encouraging efficacy in mesothelioma patients in a phase I study. To further explore the possible benefit of antibody-drug conjugate therapy for mesothelioma, we initiated a randomized, open-label, active-controlled, phase II trial to evaluate the efficacy and safety of anetumab ravtansine in patients with metastatic pleural mesothelioma (MPM) overexpressing mesothelin and who have previously progressed on platinum/pemetrexed-based first-line chemotherapy (NCT02610140). Methods: Patients (≥18 years) with unresectable locally advanced or metastatic MPM are eligible. Patients should have received ≥2 prior therapies for MPM, with the exception of patients with a histologic or cytologic diagnosis of ED-SCLC who received prior platinum doublet chemotherapy. Key inclusion criteria include: patients with ≥1 measurable lesion per RECIST v1.1; ECOG performance status of 0 or 1; ≥2 prior lines of therapy for MPM, and adequate organ function. Key exclusion criteria include: patients with a history of prior sarcoma or non-small cell lung cancer, or those with MPM who had ≥2 prior lines of therapy for MPM. Key endpoints include: overall response rate (ORR) per RECIST v1.1, duration of response, progression-free survival and overall survival. Key次要 endpoints include: time to progression (TTP), time to treatment failure, and safety.

Keywords: anetumab ravtansine, mesothelioma, immune checkpoint therapy

P2.06-029 PILOT WINDOW-OF-OPPORTUNITY STUDY OF PEMBROLIZUMAB IN PATIENTS WITH RESECTABLE MALIGNANT PLEURAL MESOTHELIOMA (MPM)

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Background: Although PD-1 inhibitors have demonstrated significant activity in MPM (Alley, WCLC 2015; Kindler, WCLC 2016), not all patients benefit. About 1/3 of MPM have high PD-L1 expression and a CD8+ infiltrative pattern with a gamma-interferon gene expression profile; this phenotype has been employed in tumors such as melanoma to predict for benefit from immune checkpoint blockade (Ribas, ASCO 2015; Seiwert, ASCO 2015). The mechanisms of anti-tumor response in a disease with a low mutational burden and DNA damage repair. Prexasertib will be administered as intravenous infusion every 2 weeks starting at 15 mg/m² and escalating to 30 mg/m². Key inclusion criteria include: patients with histologic or cytologic diagnosis of EDSCLC who received prior platinum doublet chemotherapy. Key exclusion criteria include: patients with ≥2 prior therapies for ED-SCLC, symptomatic CNS metastases, prior treatment with CHIK inhibitor, or serious cardiac conditions. Prexasertib will be administered as intravenous infusion every 14 days. Disease will be assessed by radiographic imaging every 6 weeks. Approximately 116 patients (58 per cohort) are planned for enrollment in 10 centers (<60 sites). An interim futility analysis will be conducted in each cohort after 29 patients have completed cycle 3 and, if required, the response is confirmed. Enrollment began in May 2016. Results: Not yet available.

Keywords: pembrolizumab, mesothelioma, SCLC, repilic stress
for video-thoracotomy (VATS) are required. PET/CT and VATS to obtain tissue for correlative studies are performed at baseline. Patients receive 3 cycles of pemetrexab, 200 mg IV Q21 days followed by repeat PET/CT. Extended prophylactic endotracheal intubation is performed at least 4 weeks later. Adjunct cisplatin/pemetrexed x 4 cycles is administered 6-8 weeks after surgery, followed by optional adjuvant pemetrexab x 1 year. The primary objective is to assess an increase in gamma-interferon, measured via a gene expression profile (GEP), comparing matched pre- and post-treatment samples (IFN-G Q4). Secondary outcomes to identify additional candidate biomarkers to help predict benefit or constitutive resistance to pemetrexab. Correlative studies include: a) multi-color immunofluorescence (CD8, CD4, PD-L1, FOXP3), b) evaluation of immune-related gene expression signatures (using Nanostring/RNAseq), c) evaluation of alternative immune checkpoints, d) determination of mutations in antigen presenting machinery, and e) assessment of activation of immunosuppressive signaling pathways. Radiologic correlative uses image-based texture analysis on PET/CT scans to evaluate therapy-induced changes in tumor composition. This is an exploratory trial. Fifteen patients will be enrolled, which provides a standard error for the estimated IFN-G GE response rate of approximately 10%, assuming the true response rate is close to 20%. This will also provide 80% power to detect a 0.8 standard deviation change in pre-post treatment biomarker levels, using a paired t-test at the 0.05 alpha level. Results: Section not applicable. Conclusion: Section not applicable.

Keywords: Mesothelioma, PD-1, pembrolizumab, window of opportunity trial

POSTER SESSION 2 – P2.06: SCIENTIFIC CO-OPERATION/RESEARCH GROUPS
Supportive, Preventive – TUESDAY, DECEMBER 6, 2016

P2.06-030 OPTIMUM DURATION OF VITAMIN B12/FOLATE SUPPLEMENTATION IN NSCLC PATIENTS ON PEMETREXED BASED CHEMOTHERAPY: THE PEMVITASTART RANDOMIZED TRIAL
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Background: Pemetrexed, an anti-folate drug, is the preferred chemotherapeutic agent for non-squamous NSCLC histology. Addition of vitamin B12 and folinic acid (folate; 350–1000μg PO daily) supplementation to pemetrexed containing regimens reduces the incidence and severity of myelosuppression without diminishing antitumor efficacy. Folate supplementation and vitamin B12 (1000μg intramuscular every 4–6 weeks) should be started one week before the first cycle of chemotherapy and continued for at least three weeks beyond the last cycle. However, observational and prospective single arm studies have not shown any increase in toxicity when pemetrexed was started prior to completion of the recommended vitamin B12/folate supplementation. Methods: The current study is an open-label, randomized trial (PEMVITASTART, NCT02679443) to evaluate differences in pemetrexed-related hematological toxicity amongst patients initiated on chemotherapy following 5–7 days of vitamin B12 and folate supplementation (Delayed Arm) compared to those in whom the above supplementation is started simultaneously with (within 24 hours of) chemotherapy initiation (Immediate Arm). Eligible patients are chemo-naive WITH cytologically/histopathologically proven non-squamous NSCLC AND locally advanced/metastatic (Stage IIIb/IV) disease (OR Stage IIIa not previously responded and now have failed a platinum based doublet to the previously effective therapy. Methods: In this 6-arm, 3-stage study, subjects with SCLC, NSCLC, HGNEC and ovarian cancer (EOC) in each arm receive RRx-001 weekly until progression followed by platinum therapy. Each cohort will initially enroll 13 patients to assess for safety (Stage 1) then 7 patients (Stage 2) for a total of 10 patients per cohort. If any arm has ≥10 subjects that have stable disease or better, then additional patients would be enrolled in that arm (Stage 3) for totals of 31 (NSCLC, 26 (SCLC), 26 (HGNEC) and 26 (EOC). Eligibility criteria include: evaluable, progressive disease; previous response to platinum doublet therapy; ECOG PS 0-2. Primary endpoint is Overall Survival with ORR, DCR, PFS and rate of toxicity for reintroduced platinum therapy as secondary endpoints. Exploratory pathological assessments, including oncocytic mutation expression and infiltrating tumor lymphocyte analysis, will be performed on tumor samples before and after starting the study regimens. Results: Stage 1 for all arms except EOC has been completed with no unexpected AEs. RRx-001 treatment to date resulted in a 45% (5/11) DCR including one Partial Response in HGNET. Reintroduction of platinum therapy in evaluable patients with SCLC and NSCLC resulted in an ORR of 75% (3/4), and 67% (2/3), respectively (HGNET and EOC: 0 evaluable). Median OS for all patients is 7.0 mo. (7.8 mo. median f/u). One patient with resistant SCLC had a confirmed Partial Response to cisplatin/toposide and his treatment free interval post platinum was 178 days. To date, 7 patients have been enrolled in Stage 2 and 4 patients have been enrolled in Stage 3. Recruitment to this study is continuing. Conclusion: Although the trial is ongoing, early data suggest that RRx-001 appears to increase the sensitivity of SCLC and NSCLC to subsequently reintroduced carboplatin or cisplatin (to date no HGNEC and EOC patients have been rechallenged with platinum). In addition, data from one patient indicates a conversion of resistant to sensitive SCLC phenotype. These data suggest that RRx-001 priming may lead to a new treatment strategy resulting in renewed sensitivity to chemotherapy and prolongation of survival.

Keywords: small cell lung cancer, Resensitization/reversal of resistance, non-small cell lung cancer, Immunotherapy

POSTER SESSION 2 – P2.06: SCIENTIFIC CO-OPERATION/RESEARCH GROUPS SUPPORTIVE, PREVENTIVE – TUESDAY, DECEMBER 6, 2016

P2.06-032 ORAL PIOGLITAZONE FOR THE CHEMOPREVENTION OF LUNG CANCER IN CURRENT AND FORMER SMOKERS
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Background: The development of resistance to chemotherapies in cancer leads to disease progression resulting in impaired survival. RRx-001, an ep-imunotherapeutic agent, may re-sensitize patients to previously effective, now refractory therapies, potentially improving survival. This study (NCT02489903) explores the potential of RRx-001 to sensitize patients who previously responded and now have failed a platinum based doublet to the previously effective therapy. Methods: In this 6-arm, 3-stage study, subjects with SCLC, NSCLC, HGNEC and ovarian cancer (EOC) in each arm receive RRx-001 weekly until progression followed by platinum therapy. Each cohort will initially enroll 13 patients to assess for safety (Stage 1) then 7 patients (Stage 2) for a total of 10 patients per cohort. If any arm has ≥10 subjects that have stable disease or better, then additional patients would be enrolled in that arm (Stage 3) for totals of 31 (NSCLC, 26 (SCLC), 26 (HGNEC) and 26 (EOC). Eligibility criteria include: evaluable, progressive disease; previous response to platinum doublet therapy; ECOG PS 0-2. Primary endpoint is Overall Survival with ORR, DCR, PFS and rate of toxicity for reintroduced platinum therapy as secondary endpoints. Exploratory pathological assessments, including oncocytic mutation expression and infiltrating tumor lymphocyte analysis, will be performed on tumor samples before and after starting the study regimens. Results: Stage 1 for all arms except EOC has been completed with no unexpected AEs. RRx-001 treatment to date resulted in a 45% (5/11) DCR including one Partial Response in HGNET. Reintroduction of platinum therapy in evaluable patients with SCLC and NSCLC resulted in an ORR of 75% (3/4), and 67% (2/3), respectively (HGNET and EOC: 0 evaluable). Median OS for all patients is 7.0 mo. (7.8 mo. median f/u). One patient with resistant SCLC had a confirmed Partial Response to cisplatin/toposide and his treatment free interval post platinum was 178 days. To date, 7 patients have been enrolled in Stage 2 and 4 patients have been enrolled in Stage 3. Recruitment to this study is continuing. Conclusion: Although the trial is ongoing, early data suggest that RRx-001 appears to increase the sensitivity of SCLC and NSCLC to subsequently reintroduced carboplatin or cisplatin (to date no HGNEC and EOC patients have been rechallenged with platinum). In addition, data from one patient indicates a conversion of resistant to sensitive SCLC phenotype. These data suggest that RRx-001 priming may lead to a new treatment strategy resulting in renewed sensitivity to chemotherapy and prolongation of survival.

Keywords: small cell lung cancer, Resensitization/reversal of resistance, non-small cell lung cancer, Immunotherapy

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**Abstracts**

**P2.06-033 LONG-TERM SAFETY AND EFFICACY OF DARBEPOETIN ALFA IN SUBJECTS WITH ADVANCED STAGE NSCLC RECEIVING MULTI-CYCLE CHEMOTHERAPY**

Julia García,1 Pere Gascon,1 Rajnish Nagarkar,1 Martín Smakal2, Kostas Syrigos3, Carlos Barrios4, Jesús Carlos Sánchez5, Li Zhang5, David Henry6, Alex Fleishman7, Ciso De Oliveira Brandão1

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Background: Darbepoetin alfa (DA) is an erythropoiesis-stimulating agent (ESA) that has been shown to increase hemoglobin levels and reduce the rate of transfusions in patients with chemotherapy-induced anemia (CIA). Most studies have not shown an association between ESA use and poor outcomes, but some clinical trials have reported increased mortality and/or tumor progression. This trial was therefore designed to address the safety of DA for CIA in patients with non-small cell lung cancer (NSCLC). Methods: Study 20070782 is a randomized, double-blind, noninferiority trial to compare DA with placebo in patients with NSCLC. Eligible patients are aged ≥18 years, with histologically or cytologically confirmed NSCLC, Eastern Cooperative Oncology Group (ECOG) status ≤1, stage IV NSCLC, no prior adjuvant/neoadjuvant NSCLC therapy, ≥2 cycles first-line chemotherapy planned (≥6 weeks total), and screening hemoglobin ≥11 g/dL. Approximately 3,000 patients from up to 500 global sites will be randomized 2:1 to DA (500 mcg) or placebo every 3 weeks (Q3W) until disease progression or end of chemotherapy. At hemoglobin <12 g/dL, study drug is withheld until hemoglobin ≥12 g/dL. Transfusions are allowed when necessary. Endpoints include overall survival (OS), progression-free survival (PFS), and time to worsening of performance status (KPS) of 70 or above, 1 inoperable or 2-10 brain lesions amenable to SRS, optimal standard therapy for the extracranial disease, no brain-directed therapy, no signs of significantly increased intracranial pressure, no electronic implantable devices in the brain. Treatment: Continuous TTFields at 150 kV/cm for at least 18 hours per day will be applied to the brain within 7 days of SRS. The treatment system is a portable medical device allowing normal daily activities. The device delivers TTFields to the brain using 4 Transducer Arrays, which may be covered by a wig or a hat for cosmetic reasons. Patients will receive the best standard of care for their systemic disease. Statistical Considerations: This is a prospective, randomized, multicenter, open-label study expected to recruit 270 patients. The sample size was calculated using a log-rank test (based on Lakatos 1988 and 2002) and has 80% power at a two sided alpha of 0.05 to detect a hazard ratio of 0.57. Results: Trial in progress: Conclusion: Trial in progress.

Keywords: TTFields, Tumor Treating Fields, brain metastasis, METIS

**P2.06-035 EXPLORING RECRUITMENT FACTORS IN A FEASIBILITY TRIAL OF SABR VERSUS SURGERY**

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Background: The SABRtooth trial aims to assess the feasibility of recruiting patients with stage I non-small cell lung cancer (NSCLC) to a study comparing surgery to stereotactic ablative radiotherapy (SABR). Both trial treatments were available outside of the trial. An embedded qualitative study aimed to explore reasons for non-participation or refusal to take up the randomised treatment arm in the SABRtooth trial to help identify factors that affect recruitment. Methods: Using in-depth qualitative interviews we aimed to interview sixteen patients not taking part in the trial across five sites using a pre-defined topic guide. The data were thematically analysed using a compare and contrast approach, identifying similarities and differences. Results: Fifteen patients have been approached so far for interview, ten opted out, five were interviewed. Although, from a limited sample there were three key themes affecting patients decision making: 1) influence of personal contacts 2) influence of professional contacts 3) influence of previous knowledge. We interviewed patients about their experience of being offered the trial and reasons for their treatment preferences. Patients described existing treatment preferences that were amenable to change in some cases. Their choice of treatment was subject to change throughout the process of being offered the trial and treatment options and was shaped by previous experience and knowledge. Treatment decisions were influenced by people in their close personal networks. Those that chose SABR had previous knowledge or experience of this treatment. Professionals could influence decisions by using specific phrases such as “surgery is your golden ticket” or comparing...

**POSTER SESSION 2 – P2.06: SCIENTIFIC CO-OPERATION/RESEARCH GROUPS \ SUPPORTIVE, PREVENTIVE –**

**Tuesday, December 6, 2016**

**P2.06-034 METIS: A PHASE 3 STUDY OF RADIOSURGERY WITH TTFIELDS FOR 1-10 BRAIN METASTASES FROM NSCLC**

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Background: Tumor Treating Fields (TTFields) are non-invasive regional anti-mitotic treatment modality, based on low intensity alternating electric fields. Efficacy of TTFields in metastatic brain tumors has been demonstrated in multiple in vitro and in vivo models, and in a phase I/II clinical study. TTFields treatment to the brain was shown to be safe and to extend overall survival in newly-diagnosed glioblastoma patients. Methods: 270 patients with 1-10 brain metastases (BM) from NSCLC will be randomized in a ratio of 1:1 to receive stereotactic radio surgery (SRS) followed by either TTFields or supportive care alone. Patients are followed-up every two months until 24 cerebral progression. Patients in the control arm may cross over to receive TTFields at the time of 24 cerebral progression. Objectives: To test the efficacy, safety and neurocognitive outcomes of TTFields in this patient population. Endpoints: Time to 1st cerebral progression based on the RANO-BM Criteria or neurological death (primary); time to neurocognitive failure based on the following tests: HVLT, COWAT and TMT; overall survival; radiological response rate; quality of life; adverse events severity and frequency (secondary). Main eligibility criteria: Karnofsky performance status (KPS) of 70 or above, 1 inoperable or 2-10 brain lesions amenable to SRS, optimal standard therapy for the extracranial disease, no brain-directed therapy, no signs of significantly increased intracranial pressure, no electronic implantable devices in the brain. Treatment: Continuous TTFields at 150 kV/cm for at least 18 hours per day will be applied to the brain within 7 days of SRS. The treatment system is a portable medical device allowing normal daily activities. The device delivers TTFields to the brain using 4 Transducer Arrays, which may be covered by a wig or a hat for cosmetic reasons. Patients will receive the best standard of care for their systemic disease. Statistical Considerations: This is a prospective, randomized, multicenter, open-label study expected to recruit 270 patients. The sample size was calculated using a log-rank test (based on Lakatos 1988 and 2002) and has 80% power at a two sided alpha of 0.05 to detect a hazard ratio of 0.57. Results: Trial in progress: Conclusion: Trial in progress.

Keywords: TTFields, Tumor Treating Fields, brain metastasis, METIS

**POSTER SESSION 2 – P2.06: SCIENTIFIC CO-OPERATION/RESEARCH GROUPS \ RADIOTHERAPY, TT Fields –**

**Tuesday, December 6, 2016**
the effectiveness of treatments using percentages e.g. “surgery is 100% and SABR is 99.9%.” Patients said they were happy with the way the trial was presented to them. However, they asked for time to come to terms with their diagnosis and then to be offered the trial alongside treatment options as early as possible to allow informed decision making. Conclusion: Information from interviews to date suggests that patients with NSCLC may prefer to be informed about clinical trial options at an early stage in their care pathway. This not only enables them to take account of all the information but also encourages discussion in considering when different treatment options. Treatment preferences should be explored to assess the basis for making a decision about taking part in the trial or choosing a particular treatment and to identify potential factors that could influence these decisions.

Keywords: SABR, Surgery, Recruitment, Qualitative

POSTER SESSION 2 – P2.06: SCIENTIFIC CO-OPERATION/RESEARCH GROUPS
RADIOTHERAPY, TT FIELDS – TUESDAY, DECEMBER 6, 2016

P2.06-036 LUNAR - A PHASE 3 TRIAL OF TTFIELDS IN COMBINATION WITH PD-1 INHIBITORS OR DOCETAXEL FOR 2ND LINE TREATMENT OF NON-SMALL-CELL LUNG CANCER (NSCLC)

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Background: The standard treatment for stage IIIB-N2 non-small cell lung cancer (NSCLC) is definitive chemoradiotherapy. However, the strategy for resectable IIIB-N2 disease remains controversial. This phase II multi-institutional trial (WOG15308) was designed to evaluate the feasibility of neoadjuvant chemoradiotherapy followed by surgery (tri-modality) in patients with pathologically-proven N2 NSCLC. Methods: Patients with resectable IIIA-N2 (pathologically proven N2) were eligible. Neoadjuvant chemoradiotherapy consisted of two cycles of paclitaxel (60 mg/m2) plus carboplatin consolidation chemotherapy. The primary endpoint was complete resection (R0) rate. Secondary endpoints were progression-free survival, overall survival, response rate, protocol compliance rate and morbidity/mortality.

Results: From December 2011 to November 2013, 40 patients were enrolled. The median follow-up time was 33.97 (7.2–46.3) months. The radiological response rate based on the irRC, and quality of life based on the inferiority analysis. The sample size is powered to detect a Hazard Ratio of 0.75 of TTFields-radiological response rate based on the irRC, quality of life based on the inferiority analysis. Secondary endpoints include progression-free survival, overall survival, response rate, protocol compliance rate and morbidity/mortality.

Methods: The hypothesis of the study is that the addition of TTFields to standard care second line therapies in advanced NSCLC will increase OS compared to treatment with standard second line alone. S12 patients with either squamous or non-squamous NSCLC will be enrolled in this prospective, randomized study. Patients will be stratified based on: 1) second line therapy (either PD-1 inhibitor or docetaxel), 2) history of smoking (squamous vs. non-squamous) and 3) geographical region. The main eligibility criteria are first disease progression after PD-1 inhibitor or docetaxel, histology (squamous vs. non-squamous) and geographical region. The main eligibility criteria are first disease progression after PD-1 inhibitor or docetaxel, histology (squamous vs. non-squamous) and geographical region. The main eligibility criteria are first disease progression after PD-1 inhibitor or docetaxel, histology (squamous vs. non-squamous) and geographical region.

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Methods: The hypothesis of the study is that the addition of TTFields to standard care second line therapies in advanced NSCLC will increase OS compared to treatment with standard second line alone. S12 patients with either squamous or non-squamous NSCLC will be enrolled in this prospective, randomized study. Patients will be stratified based on: 1) second line therapy (either PD-1 inhibitor or docetaxel), 2) history of smoking (squamous vs. non-squamous) and 3) geographical region. The main eligibility criteria are first disease progression after PD-1 inhibitor or docetaxel, histology (squamous vs. non-squamous) and geographical region.
Abstracts

Background: Circulating tumor cells (CTCs), which can be found in the peripheral blood of cancer patients, represent a simple and minimal-invasive source for monitoring neoplastic evolution or response to anti-cancer therapy. In recent years, numerous technology platforms for the enrichment and molecular characterization of CTCs have emerged, but comparative results and data demonstrating clinical utility are lacking for most of these platforms. To overcome this, the Innovative Medicines Initiative (IMI) consortium CANCER-ID (www.cancer-id.eu), which represents a joint undertaking of experts from academia and pharmaceutical industry, joined forces to define standards in blood-based biomarkers including the evaluation of different CTC enrichment technologies. Methods: CTC enrichment technologies including the CellSearch system, Parsortix PR1 and the Siemens filtration device were evaluated in a multicenter ring trial by using standardized spike-in samples of non-small cell lung cancer (NSCLC) cell lines, which were selected based on their different molecular characteristics and features. NSCLC cells were spiked into blood of healthy volunteers with informed consent. To increase the comparability of results, spike-in samples were generated in a centralized way following well-defined protocols for pre-analytic sample handling including sample fixation, storage and shipment. Spike-in samples were subsequently analyzed using different CTC enrichment technologies by at least three CANCER-ID partners in a blinded way according to standard operating procedures (SOPs). Results: To reflect clinically relevant disease subtypes, NSCLC cell lines were extensively profiled for copy number aberrations, mutational status (e.g. KRAS, EGFR), expression of cell surface antigens (e.g. EPCAM) as well as cell size. Based on this, cell lines with different molecular/genetic profiles were used to generate complex spike-in samples modeling the heterogeneity of real-life patient material. Spike-in samples were characterized by at least three different CANCER-ID partner laboratories using the CellSearch system, which represents the gold-standard for CTC detection and enumeration. Conclusion: IMI CANCER-ID is a public-private partnership in the field of liquid biopsies with 37 partners from 13 countries providing access to a variety of CTC enrichment technologies and patient samples. Making use of this major advantage, we describe the first efforts to establish standards in CTC enrichment and molecular characterization by generating comparative data in a multicenter ring experiment. The results will be used to improve SOPs for the analysis of patient blood samples, which represents a promising tool to monitor disease progression and/or therapeutic response. Support: IMI JU & EFPIA (grand no. 115749).

Keywords: Innovative Medicines Initiative, Circulating tumor cells, liquid biopsy

P2.06-040 WINNERS STUDY: DOES A FORMAL INTERACTIVE PATIENT EDUCATION PROGRAM POSITIVELY IMPACT PATIENT OUTCOMES AND SATISFACTION AFTER THORACIC SURGERY

Melissa Culligan1, LINDSEY BLACK, COLLEEN NORTON, SEANTRSE WIMBUSCH, CHRISTINE WELLS, FATEMeh JORSHARI, CINDY DOVE, KENDAL WILLIAMS, JAMISSON SOUTH, LAUREN TIGINI, JOSEPH FRIEDBERG, WHITNEY BURROWS, JAMES DONAHUE, SHAMUS CARR

1Thoracic Surgery, University of Maryland Medical Center, Baltimore/MD/United States of America, 2Respiratory and Physical Rehabilitation, University of Maryland Medical Center, Baltimore/United States of America, 3Nursing, University of Maryland Medical Center, Baltimore/MD/United States of America, 4Nursing, University of Maryland Medical Center, Baltimore/United States of America

Background: Post-operative complications in the thoracic surgery patient population can be costly to healthcare systems and devastating to patients and their families. The most common complications are respiratory, cardiac and gastrointestinal in nature. It is estimated that these complications occur at a rate of 3-5%. In an effort to improve patient outcomes, a nurse led multidisciplinary team developed and implemented the WINNERS Study (Walking with Integrated Nursing, Exercise, Respiratory/Rehab Services), designed to determine if a formal pre-operative/perioperative interactive patient education program would positively impact patient outcomes and improve satisfaction following thoracic surgery.

Methods:

All general thoracic surgery patients undergo informed consent and are randomized to current standard of care verbal pre-operative teaching vs a pre-operative/perioperative interactive patient education program. The multidisciplinary team developed formal patient educational materials, written and audiovisual, used to educate and prepare patients for what they should expect post-operatively with respect to the importance of secretion management, ambulation, general aspects of what to expect after surgery and the importance of their active participation in their post-operative recovery. The study design is outlined in Figure 1. The endpoints include length of stay, reintubation rates, pneumonia incidence, quality of life measurements, physical function measurements (PFT / 6min walk / total steps). Patient satisfaction is measured with the Quality of Life Instrument, SF-36 at pre-determined time-points. Results: Patients are currently actively enrolling into the study without any recruitment issues or adverse events. The preliminary analysis demonstrates a favorable impact on patient outcomes.
P2.06-041 TELENURSING: A THORACIC SURGERY NURSING INITIATIVE AIMED AT DECREASING HOSPITAL READMISSIONS AND INCREASING PATIENT SATISFACTION

Melissa Culligan1, Joseph Friedberg1, Lindsey Black1, Seanetre Wimbush1, Colleen Norton1, Whitney Burrows1, Shamus Carr1, James Donahue1, Marc Zubrow1
1Thoracic Surgery, University of Maryland Medical Center, Baltimore/MD/United States of America, 2Medicine, University of Maryland Medical Center, Baltimore/MD/United States of America

Background: In the USA there is a national initiative in healthcare to decrease hospital readmissions, decrease the cost of care while patients are hospitalized and to increase patient. A recent study evaluating mortality rates in the lung cancer resection patients reported a 30-day readmission was associated with a significant 10-fold increase in the 50-day mortality of this patient population (14.4% vs 2.5%). This report not only forces thoracic surgery teams to extend their operative mortality focus and reporting beyond the traditional 30-day time period but it also emphasizes the critical value and positive impact continued post-operative care for the first three months after discharge can have on patient outcomes. The expert care delivered by thoracic surgery nurses plays a critical role in decreasing post-operative complications and ensuring patients are safely discharged from the hospital. The valuable impact thoracic surgery nurses have on preventing hospital readmissions and improving patient satisfaction is the intended focus of this clinical trial. The positive impact telehealth interventions have on multiple different disease processes supports investigation of this care modality for the thoracic surgery patient population. We have designed a clinical trial focused on implementing a TeleNursing program with the specific aims of preventing hospital readmissions and improving patient satisfaction.

Methods: Our thoracic surgery practice currently has a “day-after-discharge” follow-up phone call program that is directed by the thoracic surgery nurses. The calls are made for patients 2-3 days after discharge and asked questions related to medications, pain management, sign or symptoms of infection, activity level and expectations, sleep, appetite and general understanding of all discharge instructions. This interaction is documented in the electronic medical record. This program has been expanded to compare the efficacy of the phone calls vs scheduled video call between nurses and patients. Patients are randomized to standard care day after discharge phone calls vs the TeleNursing follow-up video-call; discharge day 2, 1-month, 2-month and 3-month. All patients complete a patient satisfaction questionnaire at predetermined time points. The primary objective is to decrease hospital readmission rates and the secondary objective is to improve patient satisfaction. Results: Although the results of this clinical trial are pending, interim analysis indicates that patients are willing to participate in this program and are pleased with the nurse-patient interaction beyond their hospital stay. Conclusion: This clinical investigation is ongoing.

Keywords: Thoracic Nursing, Telemedicine, Thoracic Surgery, patient outcomes

P2.06-042 EVALUATE THE UTILITY OF THE COMPUTED BIOCONDUCTANCE MEASUREMENT IN THE DIAGNOSIS OF LUNG CANCER

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Background: Transcutaneous Computed Bioconductance (CB) has been shown to be different between malignant and benign lung lesions. We have launched a multicenter study to evaluate the utility of the Computed Bioconductance (CB) measurement following the CT scan in the diagnosis of lung cancer in Chinese population. Methods: In this multicenter study, we analyzed the result of a non-randomized prospective trial enrolling 123 patients with suspicious lung lesions studied by CT and CB. The pulmonary nodules or lesions confirmed by CT scan are greater than 4mm and smaller than 50mm. A CB test by BSP-E2-1000-A (Prolung Biotech Wuxi Co., Wuxi, China) was operated within these patients prior to an abnormal CT, then the tissue biopsy or surgical specimen would be conducted within 14 days. The detailed protocol could be found on ClinicalTrials.gov identifier NCT02726633. Results: Among the current 123 enrolling patients, 34 (28%) cases were diagnosed of benign lesion, and 89 (67%) cases were diagnosed of malignant lesion depend on pathological diagnosis, 6 (5%) cases were eliminated due to patient refusal of biopsy. In malignant group, 32 (30%) cases were in stage I; 17 (20%) cases were in stage II and IIIA; 30 (26%) cases were in stage IIIB and IV. In addition, 10 (12%) cases were with EGFR mutation and all were adenocarcinoma. In benign group, 2 (6%) cases were diagnosed of tuberculosis and most other were inflammation and fibrosis lesion. The sex ratio was 46/78 (female vs. male). In addition, body mass index, lung functions test, serum tumor biomarker, nodule position and appearance, medical, treatment and smoking history were collected in the study. Among all cases, 31 had concomitant PET performed and standardized uptake value were collected. Conclusion: In this enrolling study, a pre-biopsy assessment of malignant probability with a CT-detected lung lesion, the method which combined CT and CB was evaluated at first time. This non-invasive risk-stratification technology could improve the diagnostic efficacy of lung cancer.

Keywords: CT scan, lung cancer, Multicenter study, Computed bioconductance

P2.06-043 3-DIMENSIONAL HIGH THROUGHPUT MULTI-DRUG SCREENING USING PATIENT-DERIVED TUMOR CELLS (PDC) ESTABLISHED FROM SURGICAL SPECIMENS OF NSCLC

Sumin Shin1, Yong Sung Shin1, Hye Joo Choi1, Jiyeon Jung1, Jong Ho Cho1, Hong Kwan Kim1, Jeeun Lee1, Jinhoook Kim1
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Background: To investigate the clinical applicability of the high throughput screening (HTS) using patient-derived tumor cells (PDC) which were established from patients with non-small cell lung cancer undergoing surgery. Methods: PDCs were isolated and cultured from surgical specimen from NSCLC at Samsung Medical Center. We performed the HTS for 24 drugs (23 targeted agents and 1 positive control drug) with a micropillar/microwell chip platform using PDCs. Scanned images of the live cells were obtained using an optical fluorescence. With 6 dosages per drug in 7 replicates, the dose response curves and corresponding IC50 values were calculated from the scanned images. Results: From October 2015 to February 2016, 15 samples were diagnosed of lung cancer. Among them, 32 were in stage I; 17 were in stage II; 30 were in stage IIIB and IV. In addition, 10 cases were with EGFR mutation and all were adenocarcinoma. The valuable impact thoracic surgery nurses have on preventing hospital readmissions and improving patient satisfaction is the intended focus of this clinical trial. The positive impact telehealth interventions have on multiple different disease processes supports investigation of this care modality for the thoracic surgery patient population. We have designed a clinical trial focused on implementing a TeleNursing program with the specific aims of preventing hospital readmissions and improving patient satisfaction.

Methods: Our thoracic surgery practice currently has a “day-after-discharge” follow-up phone call program that is directed by the thoracic surgery nurses in the practice. Pertinent clinical details of each patient’s post-operative care are relayed to the thoracic surgery nurses. The calls are made for patients 2-3 days after discharge and asked questions related to medications, pain management, sign or symptoms of infection, activity level and expectations, sleep, appetite and general understanding of all discharge instructions. This interaction is documented in the electronic medical record. This program has been expanded to compare the efficacy of the phone calls vs scheduled video call between nurses and patients. Patients are randomized to standard care day after discharge phone calls vs the TeleNursing follow-up video-call; discharge day 2, 1-month, 2-month and 3-month. All patients complete a patient satisfaction questionnaire at predetermined time points. The primary objective is to decrease hospital readmission rates and the secondary objective is to improve patient satisfaction. Results: Although the results of this clinical trial are pending, interim analysis indicates that patients are willing to participate in this program and are pleased with the nurse-patient interaction beyond their hospital stay. Conclusion: This clinical investigation is ongoing.

Keywords: Thoracic Nursing, Telemedicine, Thoracic Surgery, patient outcomes

P2.06-044 FREQUENCY OF MUTATIONS AND RELATED FACTORS IN LUNG ADENOCARCINOMA CASES IN TURKEY

Senay Yilmaz1, Nilgun Demirtas1, Derya Karlıgöz2, Pinar Akın Kabakal1, Müzaffer Metintas1, Guntulu Ak2, Derya Karlıgöz2, Zeynep Oztürk1, Tuba Özdemirel1, Tuba Inal1
1Division of Hematology-Oncology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul/Korea, Republic of, 2Division of Hematology-Oncology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul/Korea, Republic of
Under what circumstances should limited resection be performed?

How large should resection margins be when performing limited resection?

When should a watchful waiting approach be considered?

When should radiotherapy be considered an option for primary treatment?

The entire Mount Sinai Health System network which includes 5 hospitals has started enrollment. Treatment is according to usual care but documented in the IELCART registry. Four additional health systems are in the process of joining which requires completing the enrollment application and obtaining IRB approval to submit data to the IELCART registry. Since starting in March 2015, we have enrolled over 30 participants. Actual time required by the surgeon to complete the surgical data prior to surgery is a few minutes. Time to the patient and coordinator to complete the data forms prior to surgery requires between 30 and 60 minutes. Conclusion: We anticipate that approximately 10 health care systems will ultimately enroll in the IELCART registry. Within 2 years, we anticipate starting to have statistically meaningful results in answering the relevant questions. Beyond these, the IELCART registry by continuing to collect data as part of routine clinical practice will provide an important resource to answer future questions in a timely manner as they arise, including performing studies in the neo-adjuvant setting and companion diagnostics.

Keywords: stage I, radiotherapy assessment, Surgery

POSTER SESSION 2 – P2.06: SCIENTIFIC CO-OPERATION/RESEARCH GROUPS
LAB, OTHER – TUESDAY, DECEMBER 6, 2016

P2.06-046 SHAPING AND OPTIMIZATION OF THE NON-SMALL CELL LUNG CANCER (NSCLC) DIAGNOSTIC LANDSCAPE IN AUSTRALIA AND NEW ZEALAND (ANZ)
Anchit Khanna, Mahmood Alam
Medical Affairs, Pfizer Oncology, Sydney/Australia

Background: Discovery of oncogenic genetic alterations in certain NSCLC subgroups, and their use as biomarkers and molecular targets for cancer therapy has been paradigm shifting. This has made early identification of these genetic (EGFR, KRAS, ALK, c-MET, ROS1, PI3K, HER2) mutations important for achieving better clinical outcomes. Various testing guidelines which are reviewed periodically have been unable to keep pace with the rapid technological and scientific advances in the diagnostic field. Lack of awareness and in-depth understanding of the testing guidelines may result in patients potentially missing out on the eligible targeted therapies. Methods: A literature search was conducted for molecular testing guidelines in NSCLC, which may have been published in major peer reviewed journal, presented at a conference or published in a series of focus sessions with a panel of expert surgeons, as well as a series of focus sessions with a panel of expert surgeons, as well as a series of critical questions regarding treatment of early lung cancer has been developed. Data from relevant publications from both physicians and patients pre- and post-surgery to account for potential confounders have been developed, tested, and are being entered into a web-based data collection system that also includes relevant imaging data. Sites are being registered into this new network Results: The four primary questions we found needing additional evidence that would be of most concern in regard to treatment of early lung cancer were the following:

Keywords: EGFR, ALK, Lung adenocarcinoma, ROS1

POSTER SESSION 2 – P2.06: SCIENTIFIC CO-OPERATION/RESEARCH GROUPS
LAB, OTHER – TUESDAY, DECEMBER 6, 2016

P2.06-045 INITIATIVE FOR EARLY LUNG CANCER RESEARCH ON TREATMENT (IELCART)
Raja Flores1, Claudia Henschke1, Emmanuella Taio1, David Yankelevitz2
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2Radiology, ICAHN School of Medicine at Mount Sinai, New York/United States of America

Background: Randomized controlled trial evidence to guide treatment of early stage lung cancer has been challenging for a variety of reasons. There is now increasing recognition of the power of large databases collected in the context of clinical care to provide important information and there are new statistical techniques for analysis to address unrecognized confounders. We have initiated a new multi-center, international collaborative network for this purpose. Methods: Based on an extensive literature review, scientific articles, and a series of focus sessions with a panel of expert surgeons, as well as a panel of former patients, a series of critical questions regarding treatment of early lung cancer has been developed. Data from relevant publications from both physicians and patients pre- and post-surgery to account for potential confounders have been developed, tested, and are being entered into a web-based data collection system that also includes relevant imaging data. Sites are being registered into this new network Results: The four primary questions we found needing additional evidence that would be of most concern in regard to treatment of early lung cancer were the following:

Keywords: EGFR, ALK, Lung adenocarcinoma, ROS1
and virtual media has the potential to bring consistency and uniformity in diagnosing patients with NSCLC, who are likely to benefit from targeted therapies. Finally, improvements in efficiency and TAT will inform physicians on management decisions without any unwarranted delays.

Keywords: liquid biopsy, Molecular testing algorithms, targeted sequencing, virtual reality

P2.07-001 NON-NEGOTIATED COMPANION INFLUENCE ON INFORMATION EXCHANGE AT LUNG CANCER CLINIC CONSULTATIONS

Allison Smith1, Carol Bugge2, Katherine Niven2
1Greater Glasgow and Clyde Health Board, Glasgow/United Kingdom, 2Department of Nursing and Midwifery, University of Strirling, Stirling/United Kingdom

Background: Effective information exchange is an asset to effective cancer care (Thorne et al, 2005). Lung cancer is a disease with many biomedical, physical and psychological consequences. This underlines the need for patient-centred care, tailoring communication to the specific needs, values and information preferences of each individual (Kissane et al, 2010). In the context of patient-centred care, communication with healthcare professionals can impact the effectiveness of the clinical encounter and influence clinical outcomes for patients with cancer (Aiello et al, 2008). However, the way in which healthcare professionals exchange information with patients can be affected by wide-ranging, external factors. The presence and involvement of a companion can increase the challenge and complexity of information exchange during cancer consultations (Albrecht et al, 2010). Companions add extra-dynamics to the clinical interaction and their potential to influence the exchange, either in a mediating or moderating manner warrants further investigation. As patients with lung cancer are commonly accompanied to the consultation by companions and as national and international policies advocate companion presence, research in this area is germane. Methods: Qualitative, multiple case study design. Each case centred on a patient with lung cancer. It included health professionals and patients consulted with and any accompanying companion(s). Seven cases were recruited, including 12 companions, and six professionals. Participants were recruited in 2010-2011 to outpatient clinics. Data were: consultation recordings, debrief interviews immediately post-consultation and later when policy initiatives often recommend companion presence during cancer consultations.

Keywords: mediating and moderating influence, information-exchange, non-negotiated accommodation, clinical consultations

P2.07-002 EVALUATION OF PROVIDING HEALTHCARE INFORMATION FOR LUNG MASS PATIENTS AFTER SURGERY

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1Nursing Service, Chiang Mai University, Chiang Mai/Thailand, 2Surgery, Chiang Mai University, Chiang Mai/Thailand

Background: Providing healthcare information is very important for lung mass patients after lung surgery for achieving good post-operative rehabilitation, understanding their disease, taking medication, adjusting daily life activity such as stop smoking, and health promotion. The aim of this study is to evaluate the providing healthcare information (HI) from physicians or nurses to patients to before discharged and to explore the adding discharge information needs of patients. Methods: Descriptive research with prospective data collection design was conducted. All lung mass patients undergoing lung surgery at General Thoracic Surgery Unit, Department of Surgery, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand during April 11th, 2015 to July 11th, 2016 were enrolled in this study. Lung Information Needs Questionnaire: Thai translation was provided to patients on the day before discharge date. Results:

Summary of results from LUNG from 56 patients

<table>
<thead>
<tr>
<th>Variables</th>
<th>Number of patients (n=56)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease knowledge</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Know diagnosis of disease</td>
<td>48</td>
<td>85.7</td>
</tr>
<tr>
<td>2. Know about how this disease affects lungs</td>
<td>49</td>
<td>87.5</td>
</tr>
<tr>
<td>3. Know about what is likely to happen in the future about disease recurrence, plan of follow-up and treatment</td>
<td>38</td>
<td>67.9</td>
</tr>
<tr>
<td>4. Know about what will happen over the next few years</td>
<td>47</td>
<td>83.9</td>
</tr>
<tr>
<td>Medications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Know reasons for taking inhalers or medications</td>
<td>50</td>
<td>89.3</td>
</tr>
<tr>
<td>6. Strically taking inhalers or medication according to a recommendation</td>
<td>41</td>
<td>73.2</td>
</tr>
<tr>
<td>7. Understanding about how to take inhalers or medication</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.1 Clear understand</td>
<td>34</td>
<td>60.7</td>
</tr>
<tr>
<td>7.2 Understand but need to know more</td>
<td>18</td>
<td>32.1</td>
</tr>
<tr>
<td>7.3 Slightly confused</td>
<td>3</td>
<td>5.4</td>
</tr>
<tr>
<td>7.4 Very confused</td>
<td>1</td>
<td>1.8</td>
</tr>
<tr>
<td>Self-management</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. Know that to do if a breathing gets worse</td>
<td>49</td>
<td>87.5</td>
</tr>
<tr>
<td>9. Know to call an ambulance if breathing gets worse</td>
<td>46</td>
<td>82.1</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10. Smoking status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10.1 Never smoke</td>
<td>18</td>
<td>32.1</td>
</tr>
<tr>
<td>10.2 Ex-smoker</td>
<td>36</td>
<td>64.3</td>
</tr>
<tr>
<td>10.3 Active smoker</td>
<td>2</td>
<td>3.6</td>
</tr>
<tr>
<td>Exercise</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11. Receiving advice to give up smoking</td>
<td>50</td>
<td>90.7</td>
</tr>
<tr>
<td>12. Receiving an offering to help to stop smoking</td>
<td>53</td>
<td>94.6</td>
</tr>
<tr>
<td>13. Receiving advice to some physical activities (e.g., walking, brisk walking and other kinds of exercises</td>
<td>52</td>
<td>92.9</td>
</tr>
<tr>
<td>14. Receiving advice how much physical activity should do.</td>
<td>41</td>
<td>73.2</td>
</tr>
<tr>
<td>15. How much physical activities patients did</td>
<td>2</td>
<td>3.6</td>
</tr>
<tr>
<td>16. As much as possible</td>
<td>37</td>
<td>66.0</td>
</tr>
<tr>
<td>17. Make an effort</td>
<td>16</td>
<td>28.6</td>
</tr>
<tr>
<td>18. As little as possible</td>
<td>3</td>
<td>5.4</td>
</tr>
</tbody>
</table>

There were 56 patients enrolled in this study including 18 women and 38 men. The mean age was 59.16 years (SD= 13.64). The percentage of the physicians or
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nurses who provided HI about; (1) disease knowledge was more than 80%, except disease recurrence, plan of follow-up and treatment; (2) a reason for taking inhalers or medications was 89.3%, however more than 30% of them were still not clear understand; (3) self-management was more than 75 %; (4) Giving up smoking, only 50%; (5) promoting exercise was more than 90, but 17.3 % of these were not sure what to do, (6) diet was only 62.5 %. For the open ended question, the percentage of patients who need more discharge information about disease, treatment, pain management, recurrent prevention and truth telling was 21.4 %. The percentage of patients who need more discharge information about food for post-operative lung surgery was 1.8%. Conclusion: The physicians and nurses should more provide clearly healthcare information to their patients before discharge.

Keywords: LINQ, Healthcare provider, Health Promotion

POSTER SESSION 2 – P2.07: NURSES INFORMATION FOR PATIENTS—TUESDAY, DECEMBER 6, 2016

P2.07-003 WHAT DO PEOPLE LIVING WITH AND SURVIVING LUNG CANCER AND MESOTHELIOMA WANT AND NEED FROM A RECOVERY CARE PACKAGE? Josianne Roberts
Macmillan Lung Nurse Specialist, The Rotherham NHS Foundation Trust, Rotherham/United Kingdom

Background: The National Cancer Survivorship Initiative (NCSI) was set up to improve the quality of care for people living with and beyond cancer. The NCSI specifically addresses the care for patients Living With and Beyond Cancer: Taking Action to Improve Outcomes (2013) outlines actions the NHS can take to improve the experience and care for cancer patients. A key outcome identified was the recovery package, which consists of: - an assessment of holistic needs and the development of a care plan to address these issues - a treatment summary that explains to the GP and individual what treatment has taken place and ongoing management - a cancer review by the GP within six months of diagnosis - a health and well being educational event. The generally poor prognosis for lung cancer patients is widely recognised, yet within clinical practice we are seeing more people living with lung cancer, receiving surgery and active treatments for lung cancer and many surviving over two years post diagnosis. The cancer survivorship initiative and the recovery package may be applicable to many site specific cancers and is part of the five year NHS plan but little literature, the recovery package recommendations and survey responses. Framework Analysis methods will be used. Results: Section not applicable Conclusion: Section not applicable

Keywords: recovery package, Living with, survivorship, patient experience

POSTER SESSION 2 – P2.07: NURSES DIFFERENT ASPECTS OF SYMPTOMS—TUESDAY, DECEMBER 6, 2016

P2.07-004 SOCIAL SUPPORT AND NUMBER OF SYMPTOMS ONE MONTH AFTER LUNG CANCER SURGERY Trine Oksholm, TONE RUSTOEN

Background: Background: Surgical resection is considered the treatment of choice for patients with early stage, non-small cell lung cancer. It is shown that these patients experience many concurrent symptoms after surgery. Patients with good social support experiences less emotional distress and have increased survival compared to those with poor social relationships. It is shown that lung cancer patients receives less social support than other cancer patients. However, the knowledge about surgically treated lung cancer patients’ social support is limited. There is also limited knowledge about social support influence on patients’ symptom burden. The purpose of this study was to describe patients’ experience of social support 1 month after lung cancer surgery, and to evaluate the relationship between the level of social support and number of symptoms in these patients. Methods: Patients were recruited from three university hospitals in Norway. They completed different questionnaires 1 month following surgery including; demographic and clinical characteristics, symptoms and social support. Patients’ medical records were reviewed for disease and treatment information. The Social Provisions Scale (SPS) measured social support and symptoms was measured by a multidimensional symptom assessment scale (i.e., Memorial Symptom Assessment Scale (MSAS)). Descriptive statistics were used to present demographic and clinical characteristics. The relationship between social support and number of symptoms in the nurses was analyzed by Pearson's correlation coefficient. Results: The sample consisted of 129 (57%) men and 99 (43%) women with a mean age of 65.8 years (SD 8.5, range 30 to 87). The patients experienced a relatively high level of social support (r=84.9, SD=9.4); however it was lower than the social support experienced by Norwegian breast cancer patients (r=87.96, SD=7.55). The total number of symptoms 1 month after surgery was 13 (SD 6.8). When looking into the subscales and SPS patients had the lowest score on the subscale “Opportunity for nurturance” (the support that others rely upon one for their well-being) (r=13.5, SD=8.2). Patients that experienced lower social support had a significantly higher number of symptoms (r=0.168, p=0.017). There was a significant correlation between a higher number of symptoms and social support on five of six subscales of social support. Conclusion: Findings from this study show that patients have a high number of symptoms after surgery and that patient with poor social support experiences a higher symptom burden. Clinicians need to assess patients’ social support and plan the care and follow up for the patients with low social support.

Keywords: social support, lung cancer surgery, symptoms

POSTER SESSION 2 – P2.07: NURSES DIFFERENT ASPECTS OF SYMPTOMS—TUESDAY, DECEMBER 6, 2016

P2.07-005 NARRATIVES FROM HIGH RISK RESPIRATORY PATIENTS WHO HAD BRONCHOSCOPY WITH LIMITED SEDATION AND ANALGESIA Catherine Saxen1, Fullbrook2, Kwun Fong3, Chantal Ski3
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Background: Bronchoscopy is a standard procedure to investigate and treat respiratory pathology. When patients have high risk respiratory conditions e.g. chronic obstructive pulmonary disease, the administration of sedation and analgesia is often restricted to help prevent respiratory complications. In this study, limited sedation and analgesia was given up to maximum doses of midazolam 5mg and fentanyl 100mcg. Prior to this study, the patient experience of bronchoscopy with limited sedation and analgesia was relatively unexplored. The aim of this study was to explore the patient experience of bronchoscopy with limited sedation and analgesia. Methods: A qualitative, interpretive approach was used to collect data, analyse and write up the stories of the participants in the study. Data were collected using unstructured interviews. These were transcribed then analysed phenomenologically (after Van Manen, 1990). Results: Bob was scared that he had lung cancer and required a bronchoscopy with biopsy to determine this. During the procedure Bob was aware and heard the doctors say they could not do a biopsy. This made Bob angry and frustrated. John was also aware during his bronchoscopy and remembered coughing and chocking during the procedure. John described choking as the worst feeling. Rachel was fearful that the bronchoscopy procedure would be uncomfortable and anticipated throat discomfort with coughing. Rachel expressed feeling unprepared before the procedure resulting in heightened anxiety. She also said the humour of the hospital workers helped relieve her anxiety pre-procedure. Rachel was not aware during her procedure, but suffered a sore throat and aggravation of her asthma post procedure. Conclusion: Patients’ experiences of fear dominated the findings. For example, coughing and chocking during the procedure may potentially lead to fears that they are impeding the diagnostic process. The fear that they may have lung cancer may elevate levels of anxiety and possibly impact other emotional responses, recollection of instructions and patient
education. Fear of the procedure can be reduced with caring and supportive healthcare workers. It is proposed that effective communication may promote appropriate education, support and reduce unrealistic expectations, and ease patient fears. Helpful educational material could include patient experiences of the procedure plus their acceptance of negative experiences in order to obtain a medical diagnosis. Ultimately, improved pharmaceutical interventions and anaesthetic support to improve patient experiences and manage post-procedural problems may be beneficial.

Keywords: patient experience, limited sedation and analgesia, bronchoscopy, Chronic obstructive pulmonary disease

**POSTER SESSION 2 – P2.07: NURSES DIFFERENT ASPECTS OF SYMPTOMS – TUESDAY, DECEMBER 6, 2016**

**P2.07-006 COMBINED APPLICATION OF TWO BIOLOGICAL MEDICINES WITH HEALTHCARE AND HEALTH EDUCATION IN SYSTEMIC THERAPY CLINIC**

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**Background:** The incidence of cancer increases along with the number of medicines used for the systemic healing of cancer. By using those medicines some side effects can occur. Trastuzumab could cause cardiovascular and mild conjunctivitis have emerged. All symptoms were controlled by symptomatic therapy. Skin rash of II.-III. stage appeared in January 2015, mostly on the scalp, but the patient nevertheless continued taking biological medicine. In February 2016 the skin rash was reduced after the intensity of the therapy was modulated. After receiving trastuzumab the patient only noticed mild pain in bones and muscles. Conclusion: The patient is being monitored since her first diagnosis, through surgical procedures, radiations, chemotherapy and biological medicines treatments. Through conversation and delegates to develop fundable proposals based on 2 research questions or proposal. Qualitative data indicated how participants found the day inspiring and motivating. They reported benefit from the discussion and collaboration between LCNSs, academics and research nurses. All delegates would recommend TORCH for Nursing to their colleagues. Confirmation: The evaluation to date has demonstrated the positive impact of TORCH for Nursing. Two project groups have been established with Faculty and delegates to develop fundable proposals based on 2 research questions developed during the workshops. TORCH for Nursing Workshops will be repeated in 2017 with the aim of becoming an annual event.

Keywords: Lung Oncology Nursing Research

**POSTER SESSION 2 – P2.07: NURSES RESEARCH, AUDITS – TUESDAY, DECEMBER 6, 2016**

**P2.07-008 VICTORIAN COMPREHENSIVE CANCER CENTRE LUNG CANCER CLINICAL AUDIT: COLLECTING THE UK NATIONAL LUNG CANCER AUDIT DATA FROM HOSPITALS IN AUSTRALIA**

Linda Mileskina, Tamsin Waterhouse1, Hannah Cross1, Mary Duffy1, Paula Nelson1, Mark Shaw1, Paul Mitchell1, Tim Akhurst1, Louis Irving1, Matthew Conron1, Melissa Moore2, Jennifer Philip2, Stephen Barnett2, Philip Antippa2, James Bartlett2, Jon Emery2, Jennifer Byrne2,3, Jim Bishop2,3
1Peter MacCallum Cancer Centre, Melbourne/VIC/Australia, 2Victorian Comprehensive Cancer Centre, Melbourne/VIC/Australia, 3Royal Melbourne Hospital, Melbourne/VIC/Australia, 4Austin Health, Melbourne/Australia, 5Respiratory Medicine, Royal Melbourne Hospital, Melbourne/Australia, 6Victorian 'S' Hospital, Melbourne/VIC/Australia, 7Department of Thoracic Surgery, Austin Health, Melbourne/VIC/Australia, 8Western Health, Melbourne/ACT/Australia, 9General Practice and Primary Health Care Academic Centre, University of Melbourne, Melbourne/VIC/Australia, 10Western and Central Melbourne Integrated Cancer Service, Melbourne/VIC/Australia

**Background:** Clinical audit may improve best practice within health. The UK National Lung Cancer Audit (NLCA) collects data from UK hospitals about care of patients with thoracic cancers. We aimed to replicate collection of the NLCA data elements from hospitals caring for patients with thoracic cancers within the Victorian Comprehensive Cancer Centre (VCCC) and associated Western and Central Melbourne Integrated Cancer Service (WCMICS). Methods: Retrospective audit of patients newly-diagnosed with lung cancer or mesothelioma in 2013 at 6 major VCCC or WCMICS hospitals. The objectives were to adopt/adapt the NLCA dataset for use in the Australian context; and analyze the findings using descriptive statistics to identify variations in care.
Individual data items from the NLCA were tailored to the Australian context in consultation with an expert steering committee. Data was collected from existing datasets including the Victorian Cancer Registry, Victorian Admitted Episodes Dataset and individual hospital databases. Individual medical records were audited to collect missing data. Results: 845 patients were diagnosed during 2013. Most were aged 65-80 (55%) and 62% were male. Most had non-small cell lung cancer (81%) with 9% small cell and 2% mesothelioma. Data completeness varied greatly between fields. Headline indicators of clinical care in the table below were compared to NLCA data. A significant area of concern identified was lack of access of many patients to a specialist lung cancer nurse. Conclusion:

<table>
<thead>
<tr>
<th>Benchmark</th>
<th>VCCC/WCMICS (%)</th>
<th>NLCA-2013 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with histological diagnosis</td>
<td>810/845 (96%)</td>
<td>(75%)</td>
</tr>
<tr>
<td>Patients with CT before bronchoscopy</td>
<td>384/492 (78%)</td>
<td>(91%)</td>
</tr>
<tr>
<td>NSCLC patients receiving PET scan</td>
<td>544/748 (73%)</td>
<td>(35%)</td>
</tr>
<tr>
<td>Patients with stage documented</td>
<td>518/845 (61%)</td>
<td>(93%)</td>
</tr>
<tr>
<td>Patients discussed at multidisciplinary meeting</td>
<td>585/845 (69%)</td>
<td>(96%)</td>
</tr>
<tr>
<td>Patients seen by lung cancer nurse specialist</td>
<td>110/845 (13%)</td>
<td>(84%)</td>
</tr>
<tr>
<td>Lung cancer nurse specialist present at diagnosis</td>
<td>0/845 (0%)</td>
<td>(65%)</td>
</tr>
<tr>
<td>Patients receiving active treatment</td>
<td>643/845 (76%)</td>
<td>(60%)</td>
</tr>
<tr>
<td>Patients treated with chemotherapy</td>
<td>242/845 (29%)</td>
<td>(15%)</td>
</tr>
<tr>
<td>Patients treated with chemotherapy</td>
<td>370/669 (55%)</td>
<td>(29%)</td>
</tr>
<tr>
<td>Patients treated with chest drainage</td>
<td>327/638 (51%)</td>
<td>(70%)</td>
</tr>
<tr>
<td>Patients seen by specialist palliative care</td>
<td>179/845 (21%)</td>
<td>(30%)</td>
</tr>
</tbody>
</table>

Lung cancer care at participating hospitals appeared to be comparable or better to many of the headline indicators of the NLCA. However, performing the audit retrospectively resulted in significant amounts of missing data for some fields. For future audits, prospective data collection should be harmonized across sites and correlated with survival outcomes. Initiatives to improve access to specialist lung cancer nurses are urgently needed.

Keywords: audit, lung cancer, clinical, nurses

P2.07-009 LUNG FUNCTION AFTER PULMONARY RESECTION IN LUNG CANCER
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Background: Surgical resection for lung cancer reduces the pulmonary capacity relative to the extent of the resection. The forced expiratory volume in the first second (FEV1) correlates significant to the experience of dyspnoea and lung function by the patient. In this study we analysed changes in FEV1 after thoracic surgery using the 6 minute walk test (6MWT) before and after a standardized physical exercise program. Methods: FEV1 is measured in 225 pulmonary resections (175 lobectomies, 31 pneumonectomies, 17 resections and 2 explorative thoracotomies) performed in a single surgical unit. FEV1 is measured before surgery and after 1, 2, 5 and 12 months. All patients are alive after 1 year. Patients were treated in accordance with national guidelines and 131 patients received oncologic treatment during the first year after surgery. Patients were postoperatively offered to join a physical lung rehabilitation program starting 3 to 6 weeks after surgery twice a week for 4 – 10 weeks. Results: Figure 1. First year postoperative change in FEV1

Median distance traveled after 6 minutes was 484 meters before the exercise program and 557 meters after. Change is significant; P=0.0001, paired T test). A significant reduction in FEV1 before and one month after surgery was observed, but between one month and one year after surgery no significant change was observed. Conclusion: As expected FEV1 declines after pulmonary resection for lung cancer. Physical exercise in a standardized rehabilitation program has a positive effect on the short term physical capability of the patient, but this effect is not reflected in the long term lung function test. Short intensive physical exercise after pulmonary resection in lung cancer will have an effect but sustained effects calls for fundamental and persistent efforts.

Keywords: lung cancer, lung function, Surgery, Physical rehabilitation

P2.07-010 HOSPITAL READMISSION RATES WITHIN 30 DAYS FOLLOWING THORACIC ONCOLOGY SURGERY
Maureen King, Georgina Howell, Verity Hunter
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Background: Readmission after thoracic surgery is not well documented. It impacts on patients’ physical and psychological wellbeing, whilst also increasing healthcare costs. The Thoracic Enhanced Recovery programme at Papworth Hospital (a regional cardio-thoracic centre) has reduced average length of stay from 12 days (2010) to 5 days (2014). The lung cancer nurse specialists (LCNS) were concerned that a shorter length of stay may increase the incidence of readmission. An audit was undertaken to determine the number of thoracic oncology surgical patients readmitted within 30-days of discharge. Methods: From 1st April 2015 to 31st July 2015 all surgical patients were contacted by a LCNS 30 days following discharge. A formic questionnaire including demographic, socioeconomic, surgical factors and readmission details (if appropriate) was completed. Results: 74 patients underwent surgery, 68(92%) completed the questionnaire. Of these 11(16%) were never smokers, 45(66%) ex-smokers, 12(18%) current smokers. Lobectomy was the most common operation 45(64%). Video-Assisted Thoracoscopic Surgery (VATS) accounted for 72% of all operations. 60/66 (91%) felt ready for discharge, 9/68(13%) were discharged home with a pleural drainage system, 40/64 (63%) were aware to contact LCNS for advice. Average length of stay 6.6 days, thoracotomy 7.5 days, current smokers 9 days, patients readmitted 10 days. 30 day readmission rate was 13/68(19%) of these 9(69%) were readmitted within 7 days.
Conclusion: Initially our concern was that a shorter length of stay may increase the incidence of readmission. However our findings showed that a longer length of stay (and current smoking status) was associated with an increased risk of readmission. This audit therefore suggests that enhanced recovery at Papworth Hospital is a safe and effective practice.

Recommendations

Review patient education/encourage patient self-referral for advice.

Improve discharge planning/communication with the community.

Establish a smoking cessation clinic/telephone service.

Implement a thoracoscopie to accurately identify and target the highest risk patients.

Repeat audit over a longer period.

Keywords: audit, nursing, Readmissions, Thoracic-Surgery

POSTER SESSION 2 – P.08: PATIENT SUPPORT AND ADVOCACY GROUPS

Patient's Voice, Patient's Information – TUESDAY, DECEMBER 6, 2016

P.08-001 GIVING A VOICE TO PATIENTS AND CAREGIVERS THROUGH THE LUNG CANCER CANADA 'FACES OF LUNG CANCER' SURVEY

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Background: Lung cancer (LC) is a major cause of cancer death, morbidity and loss of function. Caregivers of LC patients provide emotional, physical, and financial support, but their contribution is under-reported. The Lung Cancer Canada (LCC) Faces of Lung Cancer Survey aimed to study the impact of LC diagnosis and treatment on patients and caregivers. Methods: This 15-minute online survey for patients and caregivers was conducted in August 2015. Participants were recruited from a database of patients and caregivers, who previously consented to survey participation; targeted emails, social media postings and other patient groups were also utilized. The questionnaire covered demographics, emotional issues and stigma, symptom burden, quality of life, treatment experiences, and unmet needs. Anonymously collected results were collated by LCC. Results: Overall, 91 patients and 72 caregivers completed 163 interviews. Of surveyed patients, 57% had no active cancer. Fatigue, depression, and respiratory complaints were the most challenging symptoms for patients. Fear/uncertainty was reported as the hardest thing about LC by 40% of patients and 17% of caregivers. Most caregivers were partners (54%) or parents (38%). 60% were the primary caregiver, and 79% were former caregivers: 68% of their care receivers had died. Most caregivers coped well (79%), but stressors included care-receiver's declining health, their own emotions, and balancing responsibilities. Caregivers reported more negative feelings than patients: anxious/stressed 61%/42%, depressed/hopeless 32%/11%, cared for 13%/38%, confident/encouraged 11%/25%. Caregivers felt less support than patients from their healthcare team (75%/92%) and family/friends (65%/87%). Treatment satisfaction was lower among caregivers: only 58% felt very/somewhat satisfied (y 82% patients). 60% of patients and 68% of caregivers reported a negative stigma attached to LC. 35% of respondents felt there was less empathy toward LC than other cancers, and 38% of caregivers felt they had to advocate harder for LC than other cancers. Notably, some caregivers (8%) and patients (5%) reported a lack of compassion from medical professionals after a LC diagnosis. 37% of patients and 50% of caregivers reported a negative household financial impact from LC diagnosis. Conclusion: This report on the experiences of lung cancer patients and their caregivers highlights their reactions to the illness, and the associated prejudice and stigma. Lung Cancer Canada is working to improve patient access to supportive services, to decrease caregiver burden through support initiatives such as peer-to-peer support programs, to educate patients and caregivers on LC and their treatment options, and to advocate for LC patients in the face of established stigma.

Keywords: Caregivers, advocacy, lung cancer, stigma

POSTER SESSION 2 – P.08: PATIENT SUPPORT AND ADVOCACY GROUPS

PATIENT'S VOICE, PATIENT'S INFORMATION – TUESDAY, DECEMBER 6, 2016

P.08-002 ONLINE PATIENT EDUCATION IN ADVANCED LUNG CANCER: EFFECT ON PATIENT/CAREGIVER KNOWLEDGE

Tara Herrmann, Elaine Hamarstrom, Christine Carey

Medscape Education, Fort Sam Houston/United States of America

Background: Recent studies have found that patients with lung cancer consistently report suboptimal communication with their physicians which, in turn, can limit shared decision making and impact clinical outcomes. To address this gap, a patient/caregiver-focused educational initiative was developed to determine if online education modules could improve knowledge about treatment decisions and disease management in advanced non-small cell lung cancer (NSCLC). Methods: The initiative consisted of 4 educational activities available on WebMD Education, a website dedicated to patient/caregiver learning. Each activity included demographic questions and a pre/post-activity question to measure impact on knowledge. The activities launched online in between August and October, 2015, and data were collected through April, 2016. Results: After 9 months, a total of 8933 persons had participated in the education. Of those, 43% had lung cancer or were caregivers of a person with the disease, and 65% were female. The average age of individuals who participated in any of the 4 activities varied based on topic. Significant post-participation improvements in knowledge were observed including: 8% increase in comprehension that treatment-related side effects should be reported to their cancer care team both while on therapy and after completion of treatment with a cancer immunotherapy 16% increase in understanding the mechanism of action associated with use of cancer immunotherapies in the treatment of lung cancer (p < 0.001) 26% increase in recognizing first response with cancer immunotherapies will take longer than chemotherapy (p < 0.001) 28% increase in understanding that molecular testing is necessary in individuals with advanced NSCLC, adenocarcinoma, in order to select the most appropriate treatment Conclusion: This study demonstrates that well-designed online patient/caregiver-focused education can be successful in improving familiarity with essential elements involved in the management of advanced lung cancer. Targeted and focused digital education empowers, engages and equips patient/caregiver with information needed for self-care condition management.

Keywords: Patient Education, advanced NSCLC, molecular testing, Immunotherapy

POSTER SESSION 2 – P.08: PATIENT SUPPORT AND ADVOCACY GROUPS

PATIENT’S VOICE, PATIENT’S INFORMATION – TUESDAY, DECEMBER 6, 2016

P.08-003 QUALITY OF LIFE AND PATIENT REPORTED OUTCOME MEASURES FOR LUNG CANCER PATIENTS, TREATMENT OUTCOMES, AND PATIENT MANAGEMENT

Winfield Boerckel1, Carolyn Aldige1, Dusty Donaldson1, Hildy Grossman2, Vicki Kennedy3, Cindy Langhorne4, Susan Mantel5, Susan Rappaport6, Maureen Rigney1, Brian Tomlinson1


Background: Patients with lung cancer rank maintaining their independence and being able to care for themselves as being of greater importance than the symptoms of their disease. Quality of life (QOL) and patient reported outcomes (PRO) provide measures of patients’ physical, functional, and psychosocial wellbeing. Methods: In October 2015, advocacy organization executives met to review and evaluate the importance of QOL and PROs within the context of clinical trials and their usefulness during the care of patients with lung cancer by community oncologists. The discussion included the impact of QOL, cancer-related weight changes, diet, and exercise on patients’ overall health and advocating the importance of QOL and PRO assessments in patients with lung cancer through social media. Results: QOL and PRO measures are associated with treatment outcomes and may be useful in patient management to evaluate individual treatments and survival. Malnourishment, common in patients with lung cancer, reduces survival. Reduced appetite contributes to cancer cachexia and sarcopenia. Sarcopenia can lead to frailty, decreasing patients’ independence and tolerance and responsiveness to treatment. Early intervention to improve diet and prevent
weight loss of greater than 10% greatly improves patients' functional status and facilitates cancer treatment. Where possible, activity should be encouraged. Exercise throughout cancer treatment is safe for cancer patients and improves physical function and QOL. Information about the importance of enhanced diet and exercise and the usefulness of QOL and PROs in the management of patients with lung cancer could be shared via social media. Conclusion: Patients with lung cancer value QOL more than symptom management. Clinical trial data suggest that higher baseline QOL and PROs correlate with better disease outcome; these tools may be useful in the overall management of patients (Hollen 2014). Treatments should be evaluated based on their impact on QOL and PROs as well as survival. Weight maintenance and exercise are essential for patients overall health and QOL, and should be included in patients' treatment planning. Social media may be effective in raising awareness among patients with lung cancer and their caregivers about the importance of enhanced diet and exercise. Further discussion and research about the usefulness of QOL and PRO measures in the management of patients with lung cancer is warranted. Reference: Hollen PJ, Gralla RJ, Kris MG, et al. Measurement of quality of life in patients with lung cancer in multicenter trials of new therapies. Psychometric assessment of the Lung Cancer Symptom Scale. Cancer. 1994;73(2):2087-98.

Keywords: functional ability, independence, patient management, patient-reported outcomes

POSTER SESSION 2 - P2.08: PATIENT SUPPORT AND ADVOCACY GROUPS

PATIENT'S VOICE, PATIENT'S INFORMATION – TUESDAY, DECEMBER 6, 2016

P2.08-004 THE IMPORTANCE OF PATIENT RECALL WITHIN CANCER SURVIVORSHIP CARE FOR IMPROVED POST-TREATMENT SURVEILLANCE IN LUNG CANCER SURVIVORS

Leah Backhus1, Lynn Reinke2, David Au3, Steven Zeliadt4, Todd Edwards5

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Background: Despite widespread endorsement of survivorship cancer care plans, fewer than half of all National Cancer Institute Cancer Centers use them routinely. This may be due to inconsistent evidence linking survivorship care plans and improved cancer outcomes. We sought to examine the association between two specific survivorship care elements and patient reported quality of life and post-treatment cancer surveillance. Methods: We studied adults with Stage I or II non-small cell lung cancer having undergone surgical resection (2010-2013). The two survivorship care elements of interest were defined as cancer treatment summary and surveillance plan document in chart abstraction. Patient recall of treatment summary was further assessed by patient interview. Patient reported quality of life was assessed via telephone interview using the Functional Assessment of Cancer Therapy-Lung (FACT-L) validated survey instrument. Surveillance imaging was defined as chest CT performed 6 months following resection per NCCN guidelines and was assessed via chart abstraction. Median scores from FACT-L and subscales were compared using non-parametric equality of medians test for univariate analysis and linear regression for multivariable analysis. Surveillance rates were compared using logistic regression. All data were analyzed in STATA 13. Results: A total of 24 patients were interviewed at a median of 9.4 months (Interquartile range 2.8 months) following treatment and 16 patients consented for chart abstraction. For survivorship care elements, 77% of patients had a documented treatment summary, however only 30% of patients recalled receiving a treatment summary when interviewed. A surveillance plan was documented for 50% of patients. For patient reported quality of life, FACT-L total and subscale scores did not differ based on chart documentation of surveillance plan, treatment summary or patient recall of treatment summary. A total of 37% of patients received a post-treatment surveillance CT by 6 months from treatment. Surveillance CT was not associated with a difference in receipt of surveillance imaging however, patient recall of treatment summary was associated with increased odds of receipt of surveillance CT (OR 21.25 [95%CI 2.36-191.59, p=0.006] which persisted following adjustment for covariates (OR 24.65 [10.542.27], p=0.043). Conclusion: There is a disconnect between documentation of survivorship care and patient recall of receiving the intended information. This study suggests that efforts aimed at improving the transfer and retention of information might lead to greater adherence to guidelines and receipt of quality cancer care.

Keywords: Surveillance, survivorship, quality of life, treatment summary

POSTER SESSION 2 - P2.08: PATIENT SUPPORT AND ADVOCACY GROUPS

PATIENT'S VOICE, PATIENT'S INFORMATION – TUESDAY, DECEMBER 6, 2016

P2.08-005 TREATING CACHEXIA-ANOREXIA IN LUNG CANCER PATIENTS: UNDERSTANDING THE PATIENT PERSPECTIVE ON NOVEL TREATMENT APPROACHES

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Background: Cachexia-anorexia (CA) is a weight loss/appetite loss syndrome commonly affecting cancer patients. It is characterized by progressive sarcopenia (loss of muscle mass) accompanied by weight and appetite loss. These physiological changes lead to a decreased ability to perform daily activities, a reduction in the quality of life of the patient, and a decrease in the efficacy of chemotherapy and other treatments. Typically, oncologists focus on palliation of the symptoms of CA, and the reduction of distress of patients and families instead of on a cure. Recently, drugs that offer the possibility of treatment have shown promise in clinical trials. Methods: We conducted an online survey of lung cancer patients to understand:

- Prevalence of CA among lung cancer patients
- Extent of impairment of quality of life of lung cancer patients
- How patients are managing the symptoms of CA

The study was approved by Schulman IRB, Inc (IRB#201600600). Three hundred and thirty-five lung cancer patients were surveyed through different online platforms (social media and LUNGevity homepage). Results: Of the lung cancer patients surveyed:

- Six in ten report experiencing one or more of the physical changes asked about (unintended weight loss, loss of appetite, loss of muscle mass, and malnutrition)
- Patients currently undergoing treatment and Stage IV patients are more likely to experience these changes and be concerned than those who are not currently undergoing treatment or have less advanced lung cancer
- Unintended weight loss and other physical changes are most likely to lead to a decline in patients’ strength, energy level, and ability to engage in physical activities. Among patients who experienced a decrease in quality of life, the most important aspects they would like to improve or maintain are their energy level and their ability to remain independent
- Patients were measured in their willingness to try new treatment approaches, especially when presented with a description of the adverse events associated with treatment.

Conclusion: Cachexia-anorexia is common in lung cancer patients, including early-stage patients. Patient attitudes towards CA differ among those whose quality of life has been impaired due to weight loss and those who are able to continue living a normal life. Maintaining a sense of independence was of primary importance to all patients. Their willingness to try new treatment options, however, is based on understanding both the benefits and risks of these treatments, suggesting that a well-informed patient is more effectively engaged in their treatment decisions.

Keywords: Cachexia, benefit-risk, advocacy, anorexia

POSTER SESSION 2 - P2.08: PATIENT SUPPORT AND ADVOCACY GROUPS

PATIENT'S VOICE, PATIENT'S INFORMATION – TUESDAY, DECEMBER 6, 2016

P2.08-006 ATTEMPTS TO IMPROVE THE PATIENT LITERACY IN JAPAN

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Background: It has made it possible to live with cancer and to work with cancer, because of lung cancer treatment progress nowadays. It is indispensable for lung cancer patient effort to improve the patient's own literacy, in order to live with cancer and to work with cancer. Lung cancer patients own has been started to attempt to improve the patient force in Japan. I will report on the current situation about them. Methods: 1) Effectiveness of advocate project about ‘Working with cancer’ by National Cancer Center Japan (NCCJ) In Japan, ‘Working with cancer’ recently became an important issue in the national control plan in Japan. I have shown leadership as the secretary to support projects on ‘Working with cancer’ at the Center

Keywords: Survirovarship, quality of life, treatment summary
for Cancer Control and Information Services, NCC). This project is patient participatory. Participating patients have devised to improve patient literacy and have made it possible to work with cancer. I will clarify the difference of patient consciousness compared between patients and also discuss the project survey and interventions by Japanese Cabinet Office this year. 2) Importance of patient initiative in Japan, for the first time, the lung cancer patients groups network have launched since November on 2015 named JLCA, Japan lung cancer alliance. One of the goals of JLCA is to improve the lung cancer patient literacy in Japan. I will report JLCA activities about attempts to improve patient literacy in 2016. Results: 1) Multiple lung cancer patients have participated in the project on ‘Working with cancer’ by NCC). They had actually carried out to work together with lung cancer. Results of comparison of the two surveys between project survey by NCC) and the survey by Japanese Cabinet Office come out clearly the difference. More ambitious to work with cancer in National Cancer Center projects survey. 2) JLCA has been in cooperation with ‘The Japan Lung Cancer Society’, ‘The Japanese Society of Medical Oncology’, and enthusiastic lung cancer doctors to advocates activities especially Dr. Sawa. JLCA has been held five more seminars to improve lung cancer patient literacy at various places of Japan in 2016. Conclusion: One of the goals for Japanese lung cancer patients is to improve the patient literacy nowadays. They have ambitions to improve the patient literacy. They have participated in various activities to improve the patient literacy. It was found for them to want to be ‘Living with cancer’ and ‘Working with cancer’. The important points are two thing, effective advocates projects and trial of patient initiative. Keywords: patient initiative, patient literacy, working with cancer, Japan lung cancer alliance

P2.08-008 REGIONAL CLINICAL PATHWAY FOR LUNG CANCER IN KUMAMOTO UNIVERSITY HOSPITAL
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Background: Although half of people in Japan live in rural districts, cancer centers locate in urban area. Cancer control act was intended to accomplish equal accessibility of cancer medical care across the whole extent of Japan in 2006. According to the act, regional clinical pathways have been started to use. The aim of this study was to evaluate the pathways. Methods: Patients with lung cancer who underwent surgery in Kumamoto University Hospital between April 2010 and March 2016 were included. Candidate for the pathway of lung cancer was selected by following criteria. 1) Patient who lives far from our hospital. 2) Patient who eagers to join the pathway. Data were examined retrospectively. Patients usually visit local clinic and undergo examination at our hospital every 6 month. The medical informations are shared with patients, their family and medical staffs with hand-held chart. Results: During the study 630 lung cancer patients underwent resection in our hospital. Pathological stages of these patients were, IA in 439, IB in 90, IIA in 37, IIB in 13, IIIA in 71, IIIB in 2, and IV in 15. Of these 681 patients, 67 (11%) entered the regional clinical pathway in our hospital with mean age of 70 ± 10 years. Pathological stages of the patients who joined regional clinical pathway were, IA in 51 (12%), IB in 8 (0%), IIA in 3 (8%), IBb in 0 (0%), IIIA in 5 (7%), IIIB in 0 (0%), and IV in 0%. Mean observation period was 1083 ± 406 days (62 – 2181). Seven patients died during the study. Ten patients cancelled the pathway. The reasons why the pathway discontinued were as follows: recurrence of lung cancer in 1, other cancer occurrence in 2, patients’ own decision in 4, clinic’s issue in 5. Forty eight patients continue to use the pathway at the end of the study (72%). Mean duration of the pathway the patients used was 993 ± 481 days (3 – 2181). Mean distance between patients’ home and our hospital was 43 ± 34 km (2.6 – 144.5). Because local clinics located closed to patients’ home (mean distance: 12 ± 13 km (0.1 – 55.3), mean time they spend for attending hospital was reduced from 61 ± 41 minutes (8 – 210) to 19 ± 18 (1 – 83). Conclusion: The pathway was used in 72% patients at the end of study and reduced the time patients visiting hospital. Keywords: regional pathway, check up, Surgery, post operative state

P2.08-009 NEED FOR CONSISTENT LANGUAGE AROUND BIOMARKER TESTING IN THE DIAGNOSIS AND TREATMENT OF LUNG CANCER
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Background: Lung cancer patients now have the option of targeted therapies or immunotherapies. However, not all eligible patients are benefiting from these treatment approaches, partly due to lack of tumor testing. To determine whether inconsistent communications could be a contributor to the suboptimal biomarker testing rates, we conducted a communications audit to determine what terminology is currently being used, to come to a consensus on consistent terminology to describe the testing used to help choose lung cancer treatments. Methods: In phase I, we surveyed 28 organizations (patient advocacy organizations, pharmaceutical/testing companies, government and health sites) with the aim of identifying various terms being used to reference molecular tumor testing. In addition, in-depth interviews were conducted with 15 lung cancer patients to gain insights into their understanding of molecular testing. Results: From Phase I we discussed during a stakeholder meeting (Phase II) with 21 representatives of 11 different advocacy and pharmaceutical companies to come to agreement on terminology. Results: In Phase I, 9,379 mentions of eight different terms were inventoried (Table). Overall, there were too many terms, with inconsistent usage. Patient interviews revealed that there was disparity between the terms used to talk to health care practitioners and to patients, thereby setting up a communications gap. In the Phase II meeting, stakeholders agreed on the importance of a more unified message to achieve common understanding of molecular testing and targeted therapies. Biomarker testing was the
strong favorite. It integrates the concept of “biology” of the tumor and is more inclusive than “molecular testing,” now that PD-L1 testing is also a consideration for the new class of immunotherapy.

### Search Terms

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<th>Searched Terms</th>
<th>Pharma/BioTech</th>
<th>Testing</th>
<th>Gov’t/ Private</th>
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Conclusion: Consistent use of the term “biomarker testing” to encompass both targetable molecular mutations and PD-L1 protein expression is recommended for all stakeholders, allowing for additional elaboration on specific tests.

Keywords: molecular testing, biomarker testing, Targeted therapy, Immunotherapy

### POSTER SESSION 2 – P2.08: PATIENT SUPPORT AND ADVOCACY GROUPS

#### OTHER – TUESDAY, DECEMBER 6, 2016

#### P2.08-010 THE REACH AND ADOPTION OF A MULTIDISCIPLINARY THORACIC ONCOLOGY PROGRAM WITHIN A U.S. COMMUNITY HEALTHCARE SYSTEM

**Fedoria Rugless**, 1 Matthew Smelzer, 1 Meredith Ray, 1 Anita Patel, 1 Nana Boateng, 1 Bianca Jackson, 1 Courtney Foust, 1 Lisa Klesges, 2 Nicholas Faris, 2 Kristi Roark, 1 Sam Signore, 1 Laura Machigh, 1 Edward Robbins, 1 Raymond Osarogiagbon 1

Thoracic Oncology Research Group, Multidisciplinary Thoracic Oncology Program, Baptist Cancer Center, Memphis/TN/United States of America, 2Epidemiology and Biostatistics, University of Memphis School of Public Health, Memphis/TN/United States of America, 3Epidemiology and Biostatistics, University of Memphis School of Public Health, Memphis/TN/United States of America

Background: The Mid-South region of the US is the center of lung cancer incidence, and has a high proportion of underserved persons. We developed a multidisciplinary (MD) program for lung cancer care, involving weekly physician conferences, and a clinic in which conference-recommended treatment plans are discussed and implemented with patients. This study evaluates the reach and adoption of this program within a community healthcare system. Methods: We evaluated the reach of MD care by comparing demographic characteristics of participating patients, to the larger metropolitan and regional population of patients in a community healthcare system. Patients were referred to the program through their treating physician. Adoption was evaluated by assessing the number of physicians within each specialty who have referred patients to the MD program. Results: 550 patients were presented at MD conference, and 265 were seen at the MD clinic from 2014-2015. MD patients were younger, more likely to be female (p<0.01), and African-American (p<0.01). In patients >65 years old, the MD clinic had twice the percentage of uninsured patients (p<0.01). In patients ≥65 years old the MD clinic had a higher percentage of commercially insured patients (p<0.01 [Table]). 71 physicians referred patients to the MD conference; the greatest concentration of specialties were hematology/oncology (33%) and internal medicine (24%). Thirty-nine physicians referred patients into the MD clinic, with the greatest frequency from internal medicine (31%) and pulmonary medicine (24%). When comparing the number of active physicians by specialty, to those who referred patients into the MD conference, hematology/oncology had the greatest amount (40%), followed by pulmonary medicine (33%). For clinic referrals it was pulmonary medicine (24%), followed by hematology/oncology (13%).

Conclusion: A MD model has been implemented that can effectively reach underserved populations within the region. MD care was adopted primarily by oncologists, pulmonologists, and internists. Further efforts should be taken to expand physician adoption.

Keywords: multidisciplinary, RE-AIM, Reach, Adoption
PARTICIPATION: PRELIMINARY RESULTS

Maureen Rigney1, Kate Abramson1, Joanne Buzaglo1, Kayla Miller1, Melissa Miller1, Michelle Shwarz2

1Lung Cancer Alliance, Washington/DC/United States of America, 2Research and Training Institute, Cancer Support Community, Philadelphia/United States of America

Background: In-person support group attendance can address the greater unmet physical and emotional needs and high rates of distress experienced by those diagnosed with lung cancer. However, survivors tend to prefer lung cancer-specific groups, which can be challenging to start and maintain. As a result, there are <100 groups currently active in the US, inadequate to serve the 224,000 people diagnosed annually. The National Lung Cancer Support Group Network was established in 2015 to strengthen existing groups and form seven new groups in areas of high need. This study evaluates the psychosocial impact and benefits of group participation of the new lung cancer support groups. Methods: Using a pre/post-test design, consenting participants completed a baseline questionnaire including the CSS-15 Distress screening tool, Positive Affect Scale and Loneliness Scale prior to joining the group. After six months of attendance, follow-up was completed. The follow-up questionnaire included the CSS-15 Distress screening tool, Positive Affect and Loneliness scales and additional self-efficacy measures and 14 questions about group helpfulness. These are preliminary results from the first group at Gilda’s Club Nashville. Results: Demographics: At baseline, the participants (N=20) were mostly patients or survivors (68%), white (80%), female (64%) with an average age of 54.8. More than half reported being diagnosed at Stage IV. All were at risk for depression upon enrollment. Ten participants remained and completed the 6-month follow-up survey. Psychosocial outcomes: There was a significant decrease in overall distress (p=0.0067) following group participation but no change in positive affect or loneliness. Fewer participants reported life disruptions and feeling nervous or afraid at post-test. Eight of the follow-up participants (80%) remained at risk for depression. Group helpfulness: Eighty percent strongly agreed that after attending the group, they were better able to ask questions of their healthcare team, make treatment decisions and access information and resources. Participants felt more interested and determined after attending the group. Feelings of being isolated remained unchanged. All participants indicated that they would recommend this group to others and agreed that participation resulted in having a sense of belonging, acceptance and development of new friendships. Conclusion: Preliminary results show potential psychosocial improvements related to decreased distress, increased self-efficacy and positive benefits from group participation. Further data from this and the additional six groups will add statistical power to the findings. Study findings may provide evidence that participating in lung-cancer specific groups can be helpful in improving psychosocial outcomes.

Keywords: support groups

Change in mood scores before and after Energy therapy

<table>
<thead>
<tr>
<th>Variable (0=best 10=worst)</th>
<th>Pre-treatment mean score</th>
<th>Post-treatment mean score</th>
<th>Degree of change (p)</th>
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<tbody>
<tr>
<td>Anxiety (Do you feel anxious)</td>
<td>5.45</td>
<td>2.3</td>
<td>3.15 (&lt;0.001)</td>
</tr>
<tr>
<td>Calm (Do you feel calm)</td>
<td>4.89</td>
<td>1.71</td>
<td>3.175 (&lt;0.001)</td>
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<tr>
<td>Tension (Do you have tension in your body?)</td>
<td>5.23</td>
<td>2.16</td>
<td>3.062 (&lt;0.001)</td>
</tr>
<tr>
<td>Stress (Do you feel stressed)</td>
<td>5.46</td>
<td>2.09</td>
<td>3.375 (&lt;0.001)</td>
</tr>
<tr>
<td>Mood (Do you feel low in mood)</td>
<td>4.68</td>
<td>2.35</td>
<td>2.35 (&lt;0.001)</td>
</tr>
<tr>
<td>Pain (Are you in pain)</td>
<td>3.40</td>
<td>1.73</td>
<td>1.675 (&lt;0.001)</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>135.28</td>
<td>131.15</td>
<td>4.12 (0.007)</td>
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Conclusion: The role of complementary therapy in cancer care has long been recognized internationally and there are reports of Energy therapy used synergistically in palliative care and management of chemotherapy side effects[i]. We believe this is the first study to look at the role of complementary Energy therapy in supporting patients undergoing a cancer diagnosis. Complementary Energy therapy is a powerful tool to significantly reduce anxiety, tension and boost mood for patients undergoing investigation and treatment for lung cancer


P.02-014 LUNG CANCER AWARENESS AND BARRIERS TO PRIMARY CARE IN IRELAND

Aoife McNamara

Information Development, Irish Cancer Society, Dublin/Ireland

Background: Lung cancer is the leading cause of cancer death in both men and women in Ireland. * Previous research has shown awareness of lung cancer is high yet the majority of lung cancer patients continue to be diagnosed at an advanced stage.** In 2015 the Irish Cancer Society performed an online survey to examine the attitudes of the public in relation to the signs and symptoms of lung cancer and identify the perceived barriers for people accessing their GPs/pharmacists with symptoms. Objectives: Test awareness of prevalence, symptoms, causes and impact of lung cancer. Examine the incidence of recent interactions with health care professionals on the subject of lung health. Identify the barriers to accessing primary care for lung cancer symptoms. Examine the experiences of those who have had interactions.

Methods: Online survey of 1000 adults and booster sample of 100 smokers 65+. Sample was quota controlled on gender, age, social class and region to ensure a representative sample. Results: 47% identified lung cancer as the leading cause of cancer death in Ireland. Half of Irish adults and 31% of smokers claim to be unconcerned about being diagnosed with the disease. 79% of smokers claimed to have never spoken with a doctor/pharmacist about lung health and 59% of smokers have never spoken with a doctor/pharmacist about giving up smoking. 54% said they would not go to their doctor if they had one or more symptoms of lung cancer due to obstacles like fear (22%), expense of doctor’s visit (17%), because it is not serious enough (19%). 37% of smokers would be discouraged from visiting a doctor with symptoms.

Reasons included don’t think there is much a doctor can do for their lung health (11%), worried about what they would be told (32%), too expensive (20%) and fatalistic attitude are barriers which can influence the design of a lung cancer awareness campaign. Conclusion: This study reveals a number of barriers to early detection of lung cancer which in turn can lead to late diagnoses. These include a lack of awareness and underestimating the severity of the disease. The cost, anxiety, and fatalistic attitude are barriers which can influence the design of a lung cancer awareness campaign.

Poster Session 2 – P.02: Patient Support and Advocacy Groups other Tuesday, December 6, 2016

P.02-013 INTEGRATED COMPLEMENTARY ‘ENERGY’ THERAPY IMPROVES PATIENT EXPERIENCE OF A LUNG CANCER DIAGNOSIS

Georgia Russell, Patricia Swann, Shuna Waterman, Clare Scarlett, She Lok East and North Herts NHS Trust, Stevenage/United Kingdom

Background: 40,000 people were diagnosed with Lung cancer in the UK in 2012. Invasive procedures and repeated clinic visits compound the stress of diagnosis. This study reports a non pharmacological approach to improving patient experience. Energy therapies exist in many medical traditions healing through interaction with the patient’s biofield – the invisible psychophysical entity including the body but extending beyond it in the form of energy. In this case a technique where a trained therapist uses light touch or hands held a short distance from the subject to transfer energy to the recipient and bring a greater sense of well being. Methods: 112 patients were invited to receive an ‘Energy therapy’ session alongside their clinic appointment or bronchoscopy. The primary endpoint was reduction in anxiety. Pre and post treatment data was collected from self completed anonymous questionnaires using a 0-10 scale for subjective variables and non-invasive blood pressure recordings.

Data was analysed using a students t-test. Results: 83 patients took part in the study. 60% female, mean age 62.69. Table 1 summarises the questionnaires scores. Patients reported statistically significant reduction in anxiety, tension, stress and pain following a session of energy therapy. There was also an improvement in mood and sense of calm.

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cancer awareness campaign. Enabling health professionals and establishing accessible services to address lung health with high risk populations in a supportive manner will improve early detection of lung cancer.

Keywords: Ireland, awareness, Primary Care, Barriers

P2.08-015 PROMOTING LUNG CANCER AWARENESS IN IRELAND - BALANCING TRADITIONAL AND DIGITAL PLATFORMS
Aoife McNamara
Information Development, Irish Cancer Society, Dublin/Ireland

Background: Lung cancer is the leading cause of cancer death in Ireland, in both men and women*. Incidence of the disease continues to increase and the majority of Irish lung cancer patients are diagnosed at an advanced stage**. The Irish Cancer Society runs an annual lung cancer awareness campaign promoting awareness of the signs and symptoms and the importance of early detection. A variety of mediums are utilised including production of printed and online information, promotion via online and social media platforms and targeting the media through radio, TV, online advertorials and regional print advertising. Methods: In 2016, following previous success online, we replicated an interactive symptom checker developed by the Australian Lung Foundation. The purpose of this online tool was to promote lung cancer awareness and early detection, the public were encouraged to complete the checker and bring their results to their general practitioner (GP). The symptom checker was promoted through various media platforms and this ultimately lead to the success of the project. Results: The campaign goal was 1,720 online health checker completions (25% of benchmarked lung cancer section website visitors). Result: There were 12,185 views of the checker. 3,145 people completed the checker with 2,801 downloading the result for their GP. Conclusion: A strong call to action to the online checker was valuable as it gave a tangible action to the public. The media played a key role in promoting the campaign message to our targeted audience and contributed to the overall success of the campaign demonstrating the benefit of balancing traditional and digital platforms.

Keywords: Ireland, Digital, campaign, awareness
P3.01-001 CANCER CELL INVASION DRIVEN BY EXTRACELLULAR MATRIX REMODELING IS DEPENDENT ON THE PROPERTIES OF CANCERASSOCIATED FIBROBLASTS

Shinya Neri1, Hiroshi Date1, Masahiro Tsuboi2, Koichi Goto1, Atsushi Ochiai2, Genichiro Ishii2
1Thoracic Surgery, Kyoto University Graduate School of Medicine, Kyoto/Japan, 2Thoracic Surgery, National Cancer Center Hospital East, Kashiwa, Chiba/Japan

Background: As one form of tumor invasion, cancer cells can invade the extracellular matrix (ECM) through tracks that have been physically remodeled by cancer-associated fibroblasts (CAFs). However, CAFs are a heterogeneous population with diverse matrix-remodeling capacities. The purpose of this study is to investigate how CAFs with various matrix-remodeling capacities influence cancer cell invasion. Methods: We established single-cell-derived clones from 3 primary cultures of CAFs from lung adenocarcinoma patients (Case 1, 5 clones; Case 2, 5 clones; Case 3, 7 clones). Using a co-culture model, we evaluated the correlations between the number of invaded cancer cells and the remodeling areas generated by CAF clones in each case. Results: When A549 lung adenocarcinoma cells and CAF clones were co-cultured, both the number of invaded cancer cells and the remodeling areas generated by the CAF clones varied greatly. The number of invaded cancer cells was moderately and strongly correlated with the remodeling areas generated by each CAF clone originating from Cases 1 and 2 (R value = 0.53 and 0.68, respectively), suggesting that the remodeling areas in the ECM may determine the number of invaded cancer cells. In contrast, the number of invaded cancer cells was not correlated with the remodeling areas generated by CAF clones originating from Case 3, suggesting that factors other than the remodeling areas might determine the number of invading cancer cells. Conclusion: These findings showed two types of fibroblast-dependent cancer cell invasion that are dependent on and independent of the remodeling areas generated by CAFs.

Keywords: cancer-associated fibroblasts, tumor microenvironment, local invasion of cancer cells
resection of the right pulmonary nodules was performed (Fig. 1A-B). The patient was discharged uneventfully on postoperative day 5. Results: macroscopically, the nodules had whitish and yellowish colour, smooth margins, with tense-elastic consistency. Microscopically, an interesting bundles of spindle cells with moderate nuclear atypia organized in a fascicular pattern were clearly evident (Fig. 1F). The mitotic activity was more pronounced than previous histological samples (up to 10 mitoses/10HPF). Immunohistochemical studies showed positivity for smooth-muscle actin, desmin, and negativity for HMB-45, CD34, and TTF-1 (Ki-67-20% (Fig. 1G). Estrogen and progesterone receptor were weakly positive (Fig.1H). Based on the current criteria, a diagnosis of low-grade leiomyosarcoma was made. The patient denied the contralateral surgical resection. Eighteen months later the chest CT-scan revealed bilateral pulmonary nodules; she is currently under megestrol acetate treatment.

Conclusion: BML of the lung is a rare pathological condition with a usually indolent clinical course. Although it’s exceptional, an evolution towards a low grade leiomyosarcoma should be considered in the natural history of the disease.

Keywords: Benign metastasizing leiomyosarcoma lung

POSTER SESSION 3 – P3.01: BIOLOGY/PATHOLOGY
MORPHOLOGY – WEDNESDAY, DECEMBER 7, 2016

P3.01-006 PROGNOSTIC IMPACT OF TUMOR SPREAD THROUGH AIR SPACES IN LIMITED RESECTION FOR PSA-TAGE I LUNG CANCER
Kyohi Maša1, Aoi Sukeda2, Akihiko Yoshida3, Keisuke Asakura4, Kazuo Nakagawa1, Hiroyuki Sakurai1, Shun-Ichi Watanabe2, Hisao Asamura5, Noriko Moto6
1Pathology and Clinical Laboratories, National Cancer Center Hospital, Tokyo, Japan, 2Thoracic Surgery, National Cancer Center Hospital, Tokyo, Japan, 3Thoracic Surgery, Keio University School of Medicine, Tokyo, Japan

Background: Tumor spread through air space (STAS) is proposed as a new factor of lung cancer invasion, according to the new World Health Organization (WHO) classification. The aim of this study is to elucidate the prognostic impact and conduct a histopathological evaluation of STAS in primary lung cancer patients who underwent limited resection. Methods: We retrospectively collected 508 samples from p-Stage I primary lung cancer patients who underwent limited resection between 2004 and 2013. Hematoxylin and eosin stained tumor slides were reviewed to evaluate pathological features, including the presence or absence of STAS, and the morphological pattern in cases with STAS. We defined the pattern of STAS as single cell (SG), small cluster (SM), or large cluster (LG).

Clinicopathological characteristics and patient outcome data were collected from medical records. SPSS statistical software (IBM Corporation, Somers, NY, USA) was used for statistical analysis. Results: Histological diagnoses were 440 adenocarcinomas (Ad) (including 107 Adenocarcinoma in situ and 144 Minimally invasive adenocarcinoma), 64 squamous cell carcinomas (Sq), and 24 other types of cancer. Seventy-six cases (15.0%: 60 Ad, 9 Sq, and 7 other types of cancer) were positive for STAS. The morphological STAS patterns were 12 SG, 8 SM, and 2 LG. Seventy-six cases (15.0%: 60 Ad, 9 Sq, and 7 other types of cancer) were positive for STAS. The morphological STAS patterns were 12 SG, 8 SM, and 2 LG. Seventy-six cases (15.0%: 60 Ad, 9 Sq, and 7 other types of cancer) were positive for STAS. The morphological STAS patterns were 12 SG, 8 SM, and 2 LG. Seventy-six cases (15.0%: 60 Ad, 9 Sq, and 7 other types of cancer) were positive for STAS. The morphological STAS patterns were 12 SG, 8 SM, and 2 LG. Seventy-six cases (15.0%: 60 Ad, 9 Sq, and 7 other types of cancer) were positive for STAS. The morphological STAS patterns were 12 SG, 8 SM, and 2 LG. Seventy-six cases (15.0%: 60 Ad, 9 Sq, and 7 other types of cancer) were positive for STAS. The morphological STAS patterns were 12 SG, 8 SM, and 2 LG. Seventy-six cases (15.0%: 60 Ad, 9 Sq, and 7 other types of cancer) were positive for STAS. The morphological STAS patterns were 12 SG, 8 SM, and 2 LG. Seventy-six cases (15.0%: 60 Ad, 9 Sq, and 7 other types of cancer) were positive for STAS. The morphological STAS patterns were 12 SG, 8 SM, and 2 LG. Seventy-six cases (15.0%: 60 Ad, 9 Sq, and 7 other types of cancer) were positive for STAS. The morphological STAS patterns were 12 SG, 8 SM, and 2 LG. Seventy-six cases (15.0%: 60 Ad, 9 Sq, and 7 other types of cancer) were positive for STAS. The morphological STAS patterns were 12 SG, 8 SM, and 2 LG. Seventy-six cases (15.0%: 60 Ad, 9 Sq, and 7 other types of cancer) were positive for STAS. The morphological STAS patterns were 12 SG, 8 SM, and 2 LG. Seventy-six cases (15.0%: 60 Ad, 9 Sq, and 7 other types of cancer) were positive for STAS. The morphological STAS patterns were 12 SG, 8 SM, and 2 LG. Seventy-six cases (15.0%: 60 Ad, 9 Sq, and 7 other types of cancer) were positive for STAS. The morphological STAS patterns were 12 SG, 8 SM, and 2 LG. Seventy-six cases (15.0%: 60 Ad, 9Sq, and 7 other types of cancer) were positive for STAS. The morphological STAS patterns were 12 SG, 8 SM, and 2 LG. Seventy-six cases (15.0%: 60 Ad, 9 Sq, and 7 other types of cancer) were positive for STAS. The morphological STAS patterns were 12 SG, 8 SM, and 2 LG. Seventy-six cases (15.0%: 60 Ad, 9 Sq, and 7 other types of cancer) were positive for STAS. The morphological STAS patterns were 12 SG, 8 SM, and 2 LG. Seventy-six cases (15.0%: 60 Ad, 9 Sq, and 7 other types of cancer) were positive for STAS. The morphological STAS patterns were 12 SG, 8 SM, and 2 LG. Seventy-six cases (15.0%: 60 Ad, 9 Sq, and 7 other types of cancer) were positive for STAS. The morphological STAS patterns were 12 SG, 8 SM, and 2 LG. Seventy-six cases (15.0%: 60 Ad, 9 Sq, and 7 other types of cancer) were positive for STAS. The morphological STAS patterns were 12 SG, 8 SM, and 2 LG. Seventy-six cases (15.0%: 60 Ad, 9 Sq, and 7 other types of cancer) were positive for STAS. The morphological STAS patterns were 12 SG, 8 SM, and 2 LG. Seventy-six cases (15.0%: 60 Ad, 9 Sq, and 7 other types of cancer) were positive for STAS. The morphological STAS patterns were 12 SG, 8 SM, and 2 LG.
Background: Glomus tumor is a rare tumour that often develops in the nail bed of the exterior extremities, and accounts for 1% of all soft tissue tumors. However, they developed in the other organs, such as gastrointestinal, bone, adrenal gland, central nerve system, uterus and vagina. We here reported a rare case of a pulmonary glomus tumor with some literature. Methods: Case A 36-year-old female was admitted to our hospital with an abnormal shadow in the left lung field. She has no major disease, and smoker. The laboratory data and physical examination are normal. A chest computed tomography scan showed a nodal lesion of 1.0 cm in diameter in the left lower lobe. Thorascopic partial resection was performed. Results: The tumor was well-circumscribed lesion consists of solid sheets of tumor cells separated by capillaries and vessels of varying sizes in the pulmonary tissue. In the pathological findings, the tumor cells have relatively uniform, rounded to oval nuclei, indistinct nucleoli, and ill-defined cytoplasmatic borders. In the immunohistochemical examination, the tumor cells were positive for vimentin, HHF-35, desmin and vimentin, but negative for EMA, cytokeratinAE1/AE3, TTF-1, surfactant apoprotein A, CD34 and Factor VIII. Some tumor cells were positive for Ki-67. Those features were consistent with a pulmonary glomus tumor. Conclusion: Glomus tumor of the lung is rare tumor and only a few cases have been reported in the literature. The behavior of this neoplasm is uncertain, so the methods of diagnosis and treatment, includes of surgical approach will demand to do careful observation and further examination.

Keywords: lung tumor, glomus tumor, Thorascopic surgery

P3.01-008 CLINICOPATHOLOGICAL AND IMMUNOHISTOCHEMICAL FEATURES IN LUNG INVASIVE MUCINOUS ADENOCARCINOMA ACCORDING TO COMPUTED TOMOGRAPHY FINDINGS

Yuju Nojima, Katsuhiko Shimizu, Ai Maeda, Shin suke Saisho, Riki Okita, Masao Nakata

General Thoracic Surgery, Kawasaki Medical School, Kurashiki/Japan

Background: We performed the analysis to clarify the differences of lung invasive mucinous adenocarcinoma (IMA) based on computed tomography (CT) finding, in clinicopathological and molecular features, as well as prognosis. Methods: On the basis of CT findings, we divided lung IMA into three subtypes; solid, bubbling, and pneumonic type. We investigated differences in clinicopathological features, prognosis, and expressions of well-identified biomarkers, including CDX2, ERCC1, RRM1, Class III beta tubulin, TS, SPARC, PD-L1 and EGFR mutation, among the three subtypes. Results: A total of 29 patients of resected lung IMA were analyzed. Compared with the solid or bubbling type, the pneumonic type had a higher proportion of a symptom, large tumor size, a higher pathological stage, and a significantly worse prognosis. Immunohistochemical findings tended to be high expression in RRM1, Class III beta tubulin, Cox-2 in tumor and SPARC in stroma, but not ERCC1, TS, and PD-L1 in tumor. All biomarkers in tumor were not prognostic in RRM1, Class III beta tubulin, Cox-2 in tumor and SPARC in stroma, but not ERCC1, TS, and PD-L1 in tumor. Conclusion: Glomus tumor of the lung is rare tumor and only a few cases have been reported in the literature. The behavior of this neoplasm is uncertain, so the methods of diagnosis and treatment, includes of surgical approach will demand to do careful observation and further examination.

Keywords: lung cancer, pathology, ex-vivo artifacts, false positive diagnosis

P3.01-009 A PROSPECTIVE STUDY OF ‘SPREAD THROUGH A KNIFE SURFACE’ (STAKS) IN NON-SMALL CELL LUNG CANCER RESECTION SPECIMENS

Hans Blaauwgeers1, Douglas Flieder1, Arne Warth1, Kim Monkhorst1, Teh Ying Chou1, Birgit Witte1, Erik Thunnissen3

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Background: Spread Through Air Spaces (STAKS) is in the WHO classification considered as a form of invasion in lung adenocarcinoma. The artifactual spread of tissue fragments during lung specimen sectioning was recently described and termed Spread Through A Knife Surface (STAKS). The purpose of this study was to prospectively examine lung resection specimens for the presence and frequency of STAKS. Methods: A prospective, multi-institutional study of NSCLC lobectomy and pneumonectomy resection specimen was performed from January 1–July 1, 2016. Postsection, sampling and scoring of displaced fragments was undertaken in a systematic manner. The first cut was made with a clean long knife, the second cut was made in a parallel plane to the first cut, without cleaning the knife. Four tissue blocks were sampled: Block 1: first cut, upper part; Block 2: first cut, lower part; Block 3: second cut, upper part; Block 4: second cut, lower part. From these formalin fixed and paraffin embedded tissue blocks a superficial complete H&E stained slide was examined for the presence of displaced tissue fragments at 10x or 20x. A displaced fragment was scored as STAKS if the tissue fragment was at least 0.5 mm from the tumor or if it was on the pleural surface in the plane of the second cut. Benign and malignant STAKS were separately noted. Results: A total of 41 resection specimen were included in this study. The mean number of malignant STAKS for blocks 1-4 was 0.96, 1.44, 1.86 and 1.92, respectively and for benign STAKS the mean number was 0.11, 0.13, 0.25 and 0.25, respectively. Almost all STAKS were intra-alarveal. Comparison of malignant STAKS in block 1 (before the tumor was reached) with blocks 2-4 (containing tumor) was significant with p-values (p<0.003 Friedman’s test and post-hoc comparison p<0.005, respectively). For benign STAKS no difference was identified (p>0.23). The chance of malignant STAKS seemed to be higher when tumor was cut fresh than when cut after formalin fixation. Conclusion: The morphologic definition of STAKS is not different from STAS. This prospective study confirms the presence of benign and malignant STAKS. The presence of malignant STAKS is an artifact and increases with each and every knife cut during tissue sectioning. 1) Thunnissen et al. ArchPatholLabMed2016, 140(212-220).

Keywords: lung cancer, pathology, ex-vivo artifacts, false positive diagnosis

P3.01-010 PRIMARY GIANT CELL CARCINOMA OF THE LUNG: STUDY OF SEVEN CASES

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Background: Giant cell carcinoma (GCC) of the lung is a subtype of sarcomatoid carcinoma (2015 WHO classification) traditionally associated with a highly aggressive clinical behavior. The histology consists in giant cells without a differentiated tumor component. The aim of this study was to examine the clinical, pathological and molecular features of seven GCC cases diagnosed in our hospital. Methods: Twenty-nine sarcomatoid carcinoma diagnosed in our hospital during the years 2009-2016 were reviewed and 7 cases with GCC histology were selected for the study. Immunohistochemical staining with antibodies targeting TTF1, napsinA, p40, and β- HCG were performed. ALK and MET status were assessed by FISH. EGFR mutations were performed using real-time PCR. Results: The patients were 4 men and 3 women with a mean age of 61 years (range 45-79). At the moment of diagnosis three patients were current smokers and 4 former smokers. Five cases were peripheral tumors, six in the left lung, and one in the right lung. Complete resection was achieved in all patients. Tumor staging showed 3 cases pT1; 3 with pT2 stage and one case pT3. Histo-pathologically, all were pure GCC and immunohistochemical stains revealed that the giant cells were negative for β-HCG in all cases except one who could not be analyzed. Two cases showed null phenotype (TFF1 and p40 negative), two cases were TFF1 negative and p40 positive, two cases co-expressed TFF1 and p40 and one case was TFF1-positive and p40-negative. NapsinA was positive in two cases. Molecular analysis was done in 6 cases and no EGFR mutation was detected. FISH results for c-MET probe showed a MET/ CEN7 ratio <2 in all cases, polysomy with ≥5 MET signals without amplification was found in 5 cases. No ALK rearrangement was observed in the series. Five cases showed ALK copy number gain (3 to 5 fusion signals) and one case had two fusion signals. With a median follow-up of 38 months (5-130 months), two patients died due to brain metastases (both with vascular-luminal invasion).
and nodal metastases at the time of surgery), and five patients are alive at the moment of analysis. Conclusion: Pure GCC is a very rare lung cancer subtype and there are few series reported. Lymphovascular invasion and lymph node involvement at diagnosis can predict a worse outcome in this subtype. GCC in our series do not have a specific immunohistochemical profile. Neither EGFR nor ALK were potential molecular targets, nevertheless c-MET status could be an interesting biomarker in GCC tumors.

Keywords: Pathology, Giant cell carcinoma, cMET

P3.01-011 CLINOCOPATHOLOGICAL PROFILE AND ROLE OF IMMUNOHISTOCHEMISTRY IN THE DIAGNOSIS OF PRIMARY LUNG CANCER - A PROSPECTIVE STUDY FROM EASTERN INDIA

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Background: The clinico-pathological profile of lung cancer has changed considerably over the time in India. The histologic type also has changed from a predominant squamous histology to adenocarcinoma. We performed a prospective evaluation of primary lung cancers (PLCs) on the basis of clinical characteristics, histopathology and immunohistochemistry (IHC). Methods: The clinicohistopathological features and IHC characteristics of all PLCs (as per 2015 WHO classification) were described prospectively over a period of two years (2014-2016). The antibodies that were used were TTF-1, napsin A, P40, CK7, CK20, vimentin, synaptophysin, chromogranin, BCL-2, CD34, LCA, CD99, AFP & βHCG. Results: We have studied >400 PLCs (78.6% male and 21.4% females) with age ranging from 25 to 85 years. Most common symptoms were cough and chest pain observed in 65% of our cases. In 14.2% cases the patients primarily presented with metastasis. The most common site was brain (40%), cervical nodes (45%) and skin (15%) in our record. There were 84 cases of NSCLC and 5 cases of small cell carcinoma. 95.2% of NSCC had brain metastasis. Primary sites were 80% lung, 4% soft tissues and lymph nodes. In 39% of cases the patients primarily presented with metastasis. The most common symptoms were cough and chest pain observed in 65% of our cases. In 14.2% cases the patients primarily presented with metastasis. The most common site was brain (40%), cervical nodes (45%) and skin (15%) in our record. There were 84 cases of NSCLC and 5 cases of small cell carcinoma. 95.2% of NSCC had brain metastasis. Primary sites were 80% lung, 4% soft tissues and lymph nodes.

Keywords: Pulmonary squamous cell carcinoma, lung metastases, p40, trophoblastic tumors

P3.01-012 P40 IN METASTATIC PULMONARY TROPHOBLASTIC TUMOUR: POTENTIAL DIAGNOSTIC PITFALL WITH PULMONARY QUAMOUS CELL CARCINOMA

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Background: P40, one of the two isoforms of p63, is nowadays widely used for diagnosis of squamous cell carcinoma, especially in subtyping non-small cell carcinoma on lung biopsies. Methods: We describe a case in which lung tumour was misdiagnosed as squamous cell carcinoma due to p40 immunopositivity. Results: A 36-year-old lady presented with cough and left sided chest pain for 2 months duration. Chest imaging revealed a lesion in left lower lobe of lung and biopsy was suggestive of squamous cell carcinoma (Fig). However, past history revealed amputation of great toe for non-healing discharging ulcer which on histopathology was diagnosed as choriocarcinoma. She developed similar nodules and ulcers over the left arm, followed by a gradually worsening dry cough and progressive shortness of breath. On imaging, she was found to have a septated left sided pleural effusion. A positron emission tomography-computed tomography (PET-CT) revealed a large hypermetabolic soft tissue mass in left lower lobe with bilateral lung metastases and multiple liver deposits. On reviewing obstetric history, she also had a history of hysterecctomy five years ago, details of which were not available. Post-amputation β-hCG levels were high and she had been treated with multimodality chemotherapy for choriocarcinoma. She had good response to chemotherapy initially, however became resistant later on. Review of lung biopsy in the light of the past history along with extensive literature review led to the final diagnosis of metastatic trophoblastic tumour to lung. Figure 1: The lung biopsy shows an invasive tumour (A) (H&E, 10x); composed of polygonal cells with moderate amount of eosinophilic cytoplasm, round to oval nuclei and inconspicuous nuclei (B) (H&E, 20x). Hyaline eosinophilic material is seen amid tumour cells with mitotic activity (C) (H&E, 20x). These tumour cells show strong nuclear immunopositivity for p40 in approximately half of the tumour cells (D) (H&E, 20x). Conclusion: Hence, awareness that p40 immunopositivity can be seen in trophoblastic tumours is essential to avoid misdiagnosis, especially in sites like lung where squamous cell carcinoma is common.

Keywords: Pulmonary squamous cell carcinoma, lung metastases, p40, trophoblastic tumors

P3.01-013 CASE REPORT OF MELANOTIC SCHWANNOMA: A CHALLENGING DIAGNOSIS MADE CLEAR THROUGH GENETIC TESTING

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Background: Melanotic schwannomas (MS) are tumors associated with the Carney complex of hyperpigmentation, myxomas, and endocrine overactivity. They most frequently arise from spinal nerve roots and present a diagnostic challenge due to their lack of characteristic pathologic features. We present the case of an otherwise healthy 35-year-old man who presented with nocturnal dyspnea and ptosis. Imaging identified a large 8.1 x 9.2 x 8.4 cm mass in the right apical posterior mediastinum. Core biopsy was consistent with melanoma, although no primary site could be identified. The patient underwent complete R0 resection of an encapsulated posterior thoracic inlet mass adherent to the sympathetic chain and apical parietal pleura. Surgical pathology showed nests of large pleomorphic epithelioid cells with prominent nucleoli and abundant intracytoplasmic pigment consistent with the initial diagnosis of melanoma. The final diagnosis of melanotic schwannoma was made only when the tumor was sent for molecular testing and a rare mutation was identified. Methods: Oncogene sequencing (UCSF-Syapse) was performed on surgically resected formalin-fixed and paraffin embedded tumor. Single nucleotide variations, copy number changes, and rearrangements were detected using a hybridization-based enrichment assay of approximately 50 oncogenes commonly implicated in the development of neoplasia. Of the genes assayed, entire coding regions were analyzed in 429 genes with additional analysis of selected introns in 42 genes. Results: Based on standard hematoyxlin and eosiin (H&E) stains as well as S-100 and Melan-A positivity on immunohistochemistry (IHC) stains, the specimen was originally diagnosed as melanoma. The initial diagnosis was also supported by a Ki-67 proliferative index of 15%. Molecular testing uncovered a rare PRKARIA mutation inconsistent with melanoma and consistent with melanotic schwannoma. No other mutations were identified. PRKARIA mutations are known to occur in up to 70% of Carney complex patients but have never been known to occur in melanoma. Conclusion: Standard techniques of H&E and IHC staining with their potential to misdiagnose two similar tumor histologies are outdated in the context of 21st century technology. Modern precision medicine and molecular diagnostics enable the clear distinction of histologically similar tumors. The speed and low cost of sequencing technology has advanced to recommend its frequent use in cases such as this where a diagnosis is not entirely clear.

Keywords: Melanoma, PRKARIA, Tumor molecular sequencing, Melanotic schwannoma

P3.01-014 DIFFERENTIAL GENE EXPRESSION OF LUNG
ADENOCARCINOMA HISTOLOGY SUBTYPES ACCORDING TO THE IASLC/ATS/ERS CLASSIFICATION

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Background: The current lung cancer classification from the IASLC/ATS/ERS integrates lung invasive adenocarcinoma subtypes accounting for the clinical, radiological, molecular and prognostic differences with its implications within the clinical practice. We analyzed the differences in genetic expression of the adenocarcinoma subtypes according to the new WHO 2015 classification.

Methods: A total of 29 NSCLC patients treated at the Instituto Nacional de Cancerología of Mexico from 2008 to 2011. All patients had an available biopsy sample and were classified in four different subtypes of adenocarcinoma (2015 WHO classification). All the tissue samples were analyzed by microarrays to characterize the different expressed genes. IPA Software was used to identify biological processes, functions and biomarkers. Results: Lepidic predominant adenocarcinoma subtype was the only pattern that showed a marked gene expression difference against all predominant histological patterns, revealing genes with significant (p < 0.01) expression. For all the histological predominant pattern subtype comparisons the top functional networks were related to eight different biological categories as follows: DNA replication; Recombination and Repair; Cell Cycle; Cell Death and Survival; RNA Post-Transcriptional Modification; Cancer; Organismal Injury and Abnormalities; Cellular Development. Moreover, we observed 13 genes with specific differential expression in the Lepidic predominant adenocarcinoma subtype. Conclusion: Lepidic predominant histological pattern subtype has a differential gene expression profile when compared against all predominant histological patterns subtypes. Moreover, we found a gene expression signature of 13 genes that has a unique behavior in the Lepidic histologic pattern subtype that could be used as a specific gene expression signature, biomarker or therapeutic target.

Keywords: microarray, NSCLC, Lepidic subtype, Genetic signature

P3.01-015 PROGNOSTIC IMPACT OF HISTOLOGIC INVASION FACTORS IN PULMONARY ADENOCARCINOMA, WITH PARTICULAR FOCUS ON THE PATTERN OF ARCHITECTURAL REMODELING

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Background: In the 2015 WHO classification, histologic factors that are associated with invasion in primary lung adenocarcinoma (AdCa) include the presence of non-lepidic histologic subtypes (invasive subtypes) and the presence of cancer-associated myofibroblasts (CAF). The prognostic significance of CAFs in combination with each invasive subtype has not been well assessed. We conducted this study to clarify the prognostic impact of CAFs in the absence of architectural remodeling. Methods: We retrospectively collected data and re-evaluated samples from 1052 patients with pathological stage 0 or IA pulmonary AdCa who underwent complete resection at our hospital between 2007 and 2012. HE and elastica van Gieson stainings were used for histological evaluation. We defined two invasive subtypes: those with (INV-1) and without (INV-2) architectural remodeling of lung parenchyma. The postoperative recurrence of tumor was analyzed in each group. Results: Our reviewed diagnoses were 172 Stage 0 and 880 Stage IA AdCa. Of the 880 stage IA cases, 70% (617 cases) and 17% (149 cases) were categorized as INV-1 and INV-2, respectively. CAFs were observed in all cases in the INV-2 group, but were not always present in the INV-1 group. In the INV-2 group, the median diameter of the invasive component was 6 mm (range: 1-16), the median postoperative follow-up period was 60 months (range: 2-105), and none of the cases developed recurrence. In the INV-1 group, the median postoperative follow-up period was 55 months (range: 1-104) and the estimated 5-year recurrence-free probability by the Kaplan-Meier method was 93.0%. All cases with postoperative recurrence were categorized in the INV-1 group. Conclusion: The INV-2 group AdCa had a low risk of recurrence. These findings suggest that certain subtypes of invasive AdCa, which are classifiable based on the architectural remodeling pattern and the presence of CAF, can be considered to have a good prognosis.

Keywords: Adenocarcinoma, invasion, myofibroblast

P3.01-016 FACTORS INFLUENCING THE CONCORDANCE OF HISTOLOGICAL SUBTYPE DIAGNOSIS BY BIOPSY AND RESECTED SPECIMENS OF LUNG ADENOCARCINOMA

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Background: Lung adenocarcinoma is heterogeneous, characterized by various histological subtypes. Determination of the predominant histological subtype (lepidic, papillary, acinar or solid-predominant) has been shown to correlate with genetic abnormalities and clinicopathological features. Although subtyping using small biopsy samples is important for tailored approaches to clinical management, limited data exist on the concordance of predominant subtype between resected specimens and biopsy specimens. Methods: We compared the diagnosed predominant subtypes in resected specimens and matched biopsy specimens in a series of 327 lung adenocarcinomas. Histological subtyping of preoperative material was made by review of archived hematoxylin and eosin stain slides that had originally been prepared for diagnosis before surgery. The histological findings of surgically resected tumors was obtained from the pathological case records for each surgical resection specimen. The accuracy of preoperative diagnosis by biopsy and the factors that influence concordance with resected specimen analysis were examined. Results: In 211 of the 326 patients (66.0%), the predominant adenocarcinoma subtype was classified by biopsy matched the findings of resection analysis. Concordance rate was highest in papillary pattern (82%), followed by lepidic pattern (75%), solid pattern (66%), and acinar pattern (39%). Overall, the concordance rate in biopsy samples with larger tumor areas (≥0.7 mm²) was significantly higher than those with smaller tumor area (<0.7 mm²) 71% vs 58%, respectively; p = 0.02. Other factors in biopsy samples, such as number of biopsies, or the small biopsy type, did not have significant influence on the concordance between preoperative and postoperative diagnosis. In the biopsy samples with smaller tumor areas, the concordance rate was 77% in lepidic subtype, 71% in papillary subtype, 60% in solid subtype, and 40% in acinar subtype. Concordance rate in the biopsy samples with larger tumor area was higher in papillary and solid subtypes (88% and 76%, respectively), but remained low in acinar subtype (37%). Conclusion: These results indicate that accuracy of adenocarcinoma subtyping based on small biopsy samples is influenced by tumor area. Our study also suggests that subtyping of acinar histology using biopsy specimen is particularly error-prone.

Keywords: biopsy specimen, resected specimen, predominant subtype, lung adenocarcinoma
adenocarcinomas defined as enteric according to the 2011 International Association for the Study of Lung Cancer classification and analyzed clinical, immunohistochemical and molecular data. Immunohistochemistry (IHC) for CDX2, CK7 and TTF1 were performed and EGFR, RAS and ALK status was determined as standard procedures. Results: The series included 18 patients diagnosed and treated at our Institution between 2012 and 2015. Gastrointestinal primitive lesions were excluded using 15FDG-CT-PET and endoscopic examination. Median age was 60.5 years, patients were predominately male (M:F 12:6). More than half of patients (56%) were never or former smokers. IHC characterization identified 14 cases expressing at least one intestinal differentiation marker (CDX2 and/or CK20), while TTF1 was expressed in five cases. At time of diagnosis, 15 cases (83%) were stage IV, while 3 patients were stage II and underwent systemic treatment within one year from radical surgery. Most frequent metastatic sites were bone (44%), adrenal gland (32%) and pleura (28%). 18 exon 19-20-21 EGFR mutations were assessed in 15 patients, resulting in 3 (20%) rare mutations (exon 19 I745insKIPVA; exon 18 G719A; exon 20 S768R) and no common sensitizing EGFR mutations. No RAS or ALK alterations were found. For metastatic disease, 15 patients were able to receive first-line maintenance drugs. Two patients received platinum-based doublet (with the addition of bevacizumab in two cases), one capcetabine (n=1), two patients received EGFR inhibitors. Eight patients were able to receive second-line systemic treatment and one patient was treated with fluorouracil, oxaliplatin and bevacizumab. Three patients obtained radiological response following chemotherapy and two of them received fluoropyrimidine. Median overall survival from metastatic diagnosis was 10 (95%CI: 8-NA) months and median progression-free survival was 6 (95%CI: 2-NA) months, but great heterogeneity in outcome was noticed and third EGFR, RAS wild-type patients live more than 30 months. A high rate of late relapse or persistence of rare EGFR mutations was associated with no smoking history and worse outcome; best radiological response to EGFR inhibitors was progression. Conclusion: Primary lung enteric adenocarcinoma has heterogeneous clinical behavior and is mainly refractory to standard chemotherapy. It presents specific epidemiological features and genetic characterization is ongoing to define different subgroups and try to improve therapeutic approach. Keywords: Pathology, EGFR rare mutations, rare histology, intestinal-like adenocarcinoma

P3.01-018 REPRODUCIBILITY IN CLASSIFICATION OF SMALL LUNG ADENOCARCINOMAS: AN INTERNATIONAL INTEROBSERVER STUDY
Angela Shih, Alona Muzikansky, Eminze Bozkurtlar, Jin-Haeng Chung, Yuko Minami, Lida Hariri, Andre Moreira, Hironori Uruga, He Wang, Akiko Yoshizawa, Mari Mino-Kenudson* 
1Pathology, Massachusetts General Hospital, Boston/MA/United States of America, 2Biostatistics Center, Massachusetts General Hospital, Boston/United States of America, 3Pathology, Marmara University, Istanbul/Turkey, 4Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seoul/South Korea, 5Pathology, National Hospital Organization Ibaraki-shihigashi National Hospital, Tsukuba/Japan, 6Pathology, NYU Langone Medical Center, New York/New York/United States of America, 7Department of Respiratory Medicine, Respiratory Center, Tohosei Hospital, Tokyo/Japan, 8Pathology, Temple University School of Medicine, Philadelphia/Pennsylvania/United States of America, 9Department of Diagnostic Pathology, Kyoto University Hospital, Kyoto/Japan Background: The 2015 WHO classification for lung adenocarcinoma (ACA) provides criteria for diagnosis of adenocarcinoma in-situ (AIS), minimally invasive adenocarcinoma (MIA), and invasive adenocarcinoma (INV). Differentiating these entities can be difficult, and as understanding of prognostic significance increases, inconsistent classification is problematic. Methods: 15 cases were reviewed by an international panel of 6 lung pathologists. One slide reflecting overall morphology of each case was digitally scanned to an internet browser-based viewer. In round one, the panel independently reviewed each case to assess predominant pattern, invasive component size, and final diagnosis (AIS, MIA or INV). After a consensus conference among participants, a second round of independent review of the cases was performed. Additionally, a discussion on interpretation of elastic stain for evaluation of invasion was held. A third round of review with assessment of a concomitant elastic stain for each case was performed. Results: The intraobserver kappa coefficient ranged widely from 0.259 to 0.859. Conclusion: Interobserver agreement on diagnosis of small lung ACAs between raters was fair to moderate, with minimal improvement after a consensus conference. Inconsistent measurement of multifocal invasion, subjective interpretation of mucinous ACA have contributed to interobserver discordance. A third round of evaluation is currently ongoing to assess for improvement and the utility of elastic stains. Keywords: minimally invasive adenocarcinoma, small lung adenocarcinoma, adenocarcinoma in situ

P3.01-019 DESMOPLASIA IS ASSOCIATED WITH POOR PROGNOSIS AND CARCINOMA-ASSOCIATED FIBROBLAST HETEROGENEITY IN NON-SMALL CELL LUNG CANCER
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Princess Margaret Hospital and Ontario Cancer Institute, Toronto/ON/Canada Background: Cancer-associated fibroblasts (CAFs) are known to influence tumor development, progression and metastasis. Their characteristics and pro-invasive role in non-small cell lung cancer (NSCLC) has been recognized. However, the functional heterogeneity of CAFs between patients and its genetic basis is less understood. Methods: Two pathologists scored for desmoplasia on Hematoxylin-Eosin stained sections of resected lung tissue from two patient cohorts: one consisting of 171 NSCLC patients (128 adenocarcinoma, 43 squamous carcinoma) and the second of 24 primary cultures of CAFs. Percent area of desmoplasia among total tumor stroma was used to define high desmoplasia (HD) versus low desmoplasia (LD). The desmoplasia and survival analysis were assessed for 171 NSCLC patients. Gene expression data on RNA extracted from CAFs in contracted gels following 24 hours incubation was obtained using Illumina Human HT-12v4 Bead Chips array and was preprocessed and normalized using RMA and values were log2 transformed. Significant genes whose expression is strongly correlated (Spearman correlation coefficient and p value) with percent of desmoplasia were identified in both cohorts. The gene set enrichment analysis (GSEA) was applied to test for the enrichment of CAF cohort significant genes in 171 NSCLC cohort. Additionally, CAF significant genes were subjected to pathway enrichment analysis using Pathway Data Integration Portal version 2.5 (http://ophid.utoronto.ca/pahdir). Results: The prognosis of adenocarcinoma patients with HD had poorer outcome in comparison to the patients with LD (disease free survival at 3 years 34% vs. 75% p=0.00045 and relapse free rate 41% vs. 14%, p=0.0051). In the CAF cohort, the number of genes that are significantly associated with desmoplasia for enrichment are 356. Using GSEA, these genes were enriched in 171 NSCLC cohort (with a p value of 0.045). Protein-protein interaction (PPI) partners of these 356 genes were acquired using Integrated Interaction Database – IID (version 2016-03, http://dcv.uhres.utoronto.ca/iid/). Obtained genes were then ranked according to their degree, i.e., number of PPIs. Top 44 (top 1%) of the genes were then selected to pathway enrichment analysis using pathDIP version 2.5. 245 pathways that significantly enriched by these 44 genes (FDR < 0.01) were obtained. Many of these pathways are known to be involved in lung cancer. Conclusion: We demonstrated that the prognosis of lung adenocarcinoma patients with HD had poorer outcome in comparison to the patients with LD. Furthermore, PPI analysis of CAF genes associated with HD reveals enrichment of many cancer-related pathways, suggesting their high relevance to lung cancer. Keywords: non-small cell lung cancer, Heterogeneity, Prognosis, cancer-associated fibroblasts

P3.01-020 EVOLVING TRENDS IN LUNG CANCER PATHOLOGY
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The increased number of lung cancer falls mainly in the adenocarcinoma group. Moreover, there is a significant relative increase of adenocarcinomas corresponding with a decrease of patients with NOS and NSCC. The occurrences of the other categories, including small cell carcinoma and squamous carcinoma, have remained largely unchanged. Conclusion: The predominance of adenocarcinoma as the predominate type of lung cancer is in accordance with the global evolution. The high frequency is partly due to the trend of adenocarcinoma as the predominate type of lung cancer.

Keywords: lung cancer, Pathology

**Figure 1. Trends in lung cancer pathology (%)**

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**P3.01-021 REPRODUCIBILITY OF COMPREHENSIVE HISTOLOGIC ASSESSMENT AND REFINING HISTOLOGIC CRITERIA IN P STAGING OF MULTIPLE TUMOUR NODULES**

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**Background:** The Danish Lung Cancer Registry has since 2003 reported all cases of lung cancer in Denmark including the pathology. We present the trends over time in the distribution of subgroups of pathology. Methods: All Danish lung cancer patients are ascertained based on coded information in the National Patient Register. Supplementary information for each patient is obtained from the clinical units as well as from the National Pathology Register (NPR). Based on SNOMED coding the patients is categorized in 12 subgroups of lung cancer. Results: Table 1. Distribution of pathology subgroups, n = 56,554.

<table>
<thead>
<tr>
<th>Year</th>
<th>No pathology</th>
<th>Small cell carcinoma (SCLC)</th>
<th>Large cell neuroendocrine carcinoma</th>
<th>Non-small cell carcinoma (NSCC)</th>
<th>Squamous carcinoma</th>
<th>Adeno carcinoma</th>
<th>Neuroendocrine tumor</th>
<th>Carcinoid tumor</th>
<th>Not otherwise specified (NOS)</th>
<th>Mixed tumor</th>
<th>Sum</th>
</tr>
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<tr>
<td>2003</td>
<td>411</td>
<td>546</td>
<td>10</td>
<td>482</td>
<td>615</td>
<td>844</td>
<td>26</td>
<td>6</td>
<td>545</td>
<td>107</td>
<td>3.667</td>
</tr>
<tr>
<td>2004</td>
<td>407</td>
<td>585</td>
<td>3</td>
<td>555</td>
<td>636</td>
<td>786</td>
<td>30</td>
<td>10</td>
<td>533</td>
<td>109</td>
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<td>2005</td>
<td>354</td>
<td>668</td>
<td>19</td>
<td>562</td>
<td>620</td>
<td>953</td>
<td>31</td>
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<td>537</td>
<td>116</td>
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<td>2006</td>
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<td>266</td>
<td>26</td>
<td>577</td>
<td>713</td>
<td>963</td>
<td>26</td>
<td>2</td>
<td>463</td>
<td>114</td>
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<td>15</td>
<td>580</td>
<td>710</td>
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<td>26</td>
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<td>666</td>
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<td>36</td>
<td>16</td>
<td>415</td>
<td>144</td>
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<tr>
<td>2009</td>
<td>434</td>
<td>711</td>
<td>12</td>
<td>690</td>
<td>742</td>
<td>1,248</td>
<td>33</td>
<td>13</td>
<td>358</td>
<td>154</td>
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<td>2010</td>
<td>397</td>
<td>699</td>
<td>11</td>
<td>744</td>
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<td>37</td>
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<td>140</td>
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<td>378</td>
<td>698</td>
<td>10</td>
<td>774</td>
<td>720</td>
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<td>30</td>
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<td>260</td>
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<tr>
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<td>342</td>
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<td>793</td>
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<td>712</td>
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<td>641</td>
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<td>2015</td>
<td>399</td>
<td>674</td>
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<td>595</td>
<td>847</td>
<td>1,782</td>
<td>15</td>
<td>5</td>
<td>177</td>
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Abstracts Journal of Thoracic Oncology • Volume 12 Issue S1 January 2017
Background: Multiple tumor nodules (MTNs) are being encountered, with increasing frequency with the 8th TNM staging system recommending classification as separate primary lung cancers (SPLC) or intrapulmonary metastases (IM). Pathological staging requires classification of morphological features, with criteria of Martini and Malmed supplemented by comprehensive histologic assessment of tumour type, predominant pattern, other histologic patterns and cytologic features. With publication of the 2015 WHO classification of lung tumours, a comprehensive histologic assessment and also sought to identify the most useful histological features. Methods: We conducted an online survey in which pathologists reviewed a sequential cohort of resected multifocal tumours to determine whether they were SPLC, IM, or a combination. Specific histological features for each nodule were entered into the database by the observing pathologist (tumour type, predominant adenocarcinoma pattern, and histological features including presence of lepidic growth, intra-alveolar cell clusters, cell size, mitotic rate, nuclear pleomorphism, nucleolar size and pleomorphism, nuclear inclusions, necrosis pattern, vascular invasion, mucin content, keratinization, clear cell change, cytoplasmic granules, lymphocytosis, macrophage response, acute inflammation and emperipolesis). Results were statistically analyzed for concordance with submitting diagnosis (gold standard) and among pathologists. Consistency of each feature was correlated with final determination of SPLC vs IM status (p staging) by chi square analysis and other tests. Results: Seventeen pathologists evaluated 126 tumors from 48 patients. Kappa score on overall assessment of primary vs metastatic status was 0.60. There was good agreement as measured by Cohen’s Kappa (0.64, p<0.0001) between WHO histological patterns in individual cases with SPLC or IM status but proportions for histology and SPT or IM status were not identical (Kappa’s test, p=0.001). Additional histological features were assessed. There was marked variation in values among the specific histological features. The strongest correlations (p<0.05) between p staging status and histological features were with nuclear pleomorphism, cell size, acinus formation, necrotic size, mitotic rate, nuclear inclusions, intra-alveolar clusters and necrosis pattern. Correlation between lymphocytosis, mucin content, lepidic growth, vascular invasion, macrophage response, clear cell change, acute inflammation keratinization and emperipolesis did not reach a p value of 0.05. Conclusion: Comprehensive histologic assessment shows good reproducibility between practicing lung pathologists. In addition to tumour type and predominant patterns, nuclear pleomorphism, cell size, acinus formation, necrotic size, and mitotic rate appear to be useful in distinguishing between SPLC and IM.

Keywords: lung cancer, Pathology, Staging, multiple tumours


P3.01-022 IMPACT OF HISTOLOGIC SUBTYPE AND SPREAD THROUGH AIR SPACES (STAS) IN STAGE III (N2) LUNG ADENOCARCINOMA

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Background: Approximately 15% of patient with non-small cell lung cancer (NSCLC) is present with stage III (N2) disease. The patient prognosis after complete resection for pathological N2 NSCLC remains a significant concern. Currently, the new WHO's TNM classification and subclassification of morphological features was revised and newly prescribed to describe the presence of each histologic subtype in adenocarcinoma (ADC) and the Spread Through Air Spaces (STAS). The purpose of this study is to examine the relationship between histologic subtypes and spread of tumour, especially STAS, lymphocytic, macrophage infiltration, and clinicopathologic features of STAS in stage III (N2) lung ADC according to new WHO classification retrospectively. Methods: All available tumor slides from 48 patients with pathological N2, surgically resected lung ADC (1998-2013) were reviewed. Each tumor was evaluated by comprehensive histologic subtyping for each nodule were entered into the database by the observing pathologist (tumour type, predominant adenocarcinoma pattern, and histological features including presence of lepidic growth, intra-alveolar cell clusters, cell size, mitotic rate, nuclear pleomorphism, nucleolar size and pleomorphism, nuclear inclusions, necrosis pattern, vascular invasion, mucin content, keratinization, clear cell change, cytoplasmic granules, lymphocytosis, macrophage response, acute inflammation and emperipolesis). Results were statistically analyzed for concordance with submitting diagnosis (gold standard) and among pathologists. Consistency of each feature was correlated with final determination of SPLC vs IM status (p staging) by chi square analysis and other tests. Results: Seventeen pathologists evaluated 126 tumors from 48 patients. Kappa score on overall assessment of primary vs metastatic status was 0.60. There was good agreement as measured by Cohen’s Kappa (0.64, p<0.0001) between WHO histological patterns in individual cases with SPLC or IM status but proportions for histology and SPT or IM status were not identical (Kappa’s test, p=0.001). Additional histological features were assessed. There was marked variation in values among the specific histological features. The strongest correlations (p<0.05) between p staging status and histological features were with nuclear pleomorphism, cell size, acinus formation, necrotic size, mitotic rate, nuclear inclusions, intra-alveolar clusters and necrosis pattern. Correlation between lymphocytosis, mucin content, lepidic growth, vascular invasion, macrophage response, clear cell change, acute inflammation keratinization and emperipolesis did not reach a p value of 0.05. Conclusion: Comprehensive histologic assessment shows good reproducibility between practicing lung pathologists. In addition to tumour type and predominant patterns, nuclear pleomorphism, cell size, acinus formation, necrotic size, and mitotic rate appear to be useful in distinguishing between SPLC and IM.

Keywords: lung cancer, Pathology, Staging, multiple tumours, lymphocytic, macrophage infiltration, Spread Through Air Spaces (STAS)
ones is thought to be tightly regulated by several microenvironmental factors. The aim of this study was to elucidate the morphological and phenotypical differences between micrometastatic and macrometastatic tumors. Methods: We first examined the morphological characteristics of 66 lymph node (LN) micrometastatic tumors (less than 2 mm in size) and 51 macrometastatic tumors (more than 10 mm in size) in 42 lung adenocarcinoma cases. Then, we evaluated the expression level of E-cadherin, S100A4, ALDH1, and Geminin in cancer cells and the number of smooth muscle actin (SMA), CD34, and CD204 (+) stromal cells in the primary tumors, matched micrometastatic tumors, and macrometastatic tumors (n = 34, each). Results: Tumor budding reflects the process of EMT, and stromal reactions were observed more frequently in macrometastatic tumors (P < 0.001). E-cadherin staining score for the micrometastatic tumors was significantly higher than that for the primary tumors (P < 0.001). In contrast, the E-cadherin staining score for the macrometastatic tumors was significantly lower than that for the micrometastatic tumors (P = 0.017). As for the stromal cells, the numbers of SMA (+) fibroblasts, CD34 (+) microvessels, and CD204 (+) macrophages were significantly higher for the macrometastatic tumors and primary tumors than for the micrometastatic tumors (P < 0.001, all). Conclusion: The present study clearly showed that dynamic microenvironmental changes (e.g., EMT-related changes in cancer cells and structural changes in stromal cells) occur during the growth of micrometastases into macrometastases.

Keywords: micrometastasis, microenvironmental changes, lung adenocarcinoma, lymph node metastasis

POSTER SESSION 3 – P3.01 BIOLOGY/PATHOLOGY MORPHOLOGY – WEDNESDAY, DECEMBER 7, 2016

P3.01-025 PRIMARY PULMONARY SARCOMAS: AN ENTITY LOST IN MISDIAGNOSIS
Kavneet Kaur,1 Deepali Jain,2 Sameer Rastogi,3 Sunil Kumar,4 Karan Madan5
1Pathology, All India Institute of Medical Sciences, New Delhi, New Delhi/India, 2Pathology, All India Institute of Medical Sciences, New Delhi/India, 3All India Institute of Medical Sciences, New Delhi, New Delhi/India, 4Surgical Oncology, All India Institute of Medical Sciences, New Delhi/India, 5Pulmonary and Sleep Medicine, All India Institute of Medical Sciences, New Delhi, New Delhi/India

Background: Primary pulmonary sarcomas are very rare with an incidence rate of <0.5% of all lung malignancies. Their low incidence has impeded comprehensive evaluation of their association with smoking, definitive diagnostic and treatment regimes. They are often misdiagnosed, both on radiology as well as on fine-needle-aspirate/small-biopsies. We present a series of primary pulmonary sarcomas diagnosed over the last two and a half years. Methods: All cases of primary pulmonary sarcomas (2014-2016) were retrieved and reviewed.

Results: A total of 21 sarcomas were identified. The most common was synovial sarcoma. Four exceptionally rare cases included pulmonary-artery intimal sarcoma, primary pulmonary myxoid sarcoma, malignant peripheral nerve-sheath tumor and follicular dendritic-cell sarcoma. The clinical and pathology details of which are provided in table1. The patients were distributed over a wide-age range (range:9-65 years, median:34 years) with a male-preponderance (M:F=2.2:1). Radiological features were non-specific except in case1(table1). Histopathology revealed spindle-cell tumor in all cases(figure1) and an extensive immunohistochemical-panel and cytogenetic testing was required to clinch the diagnosis.

Keywords: sarcoma, pulmonary, Primary, Immunohistochemistry

Table 1: Clinical, radiological and pathological details of patients with primary pulmonary sarcomas

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Sex</th>
<th>Pathology</th>
<th>Presenting symptom</th>
<th>Duration</th>
<th>Imaging</th>
<th>Histology</th>
<th>Cytogenetic</th>
<th>Treatment</th>
<th>Follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>34</td>
<td>M</td>
<td>Synovial</td>
<td>Cough</td>
<td>1 year</td>
<td>EBUS-TBNA</td>
<td>Synovial</td>
<td></td>
<td>Partial response</td>
<td>and description</td>
</tr>
<tr>
<td>2.</td>
<td>35</td>
<td>F</td>
<td>Myxoid</td>
<td>Cough, chest pain</td>
<td>7 months</td>
<td>Endobronchial biopsy</td>
<td>Myxoid</td>
<td></td>
<td>Complete response</td>
<td>and description</td>
</tr>
<tr>
<td>3.</td>
<td>46</td>
<td>F</td>
<td>Intimal</td>
<td>Dyspnea, hemoptysis</td>
<td>6 months</td>
<td>EBUS biopsy</td>
<td>Intimal</td>
<td></td>
<td>Progressive disease</td>
<td>and description</td>
</tr>
<tr>
<td>4.</td>
<td>47</td>
<td>F</td>
<td>Dendritic</td>
<td>Right side chest pain</td>
<td>3 months</td>
<td>EBUS-CORE biopsy</td>
<td>Dendritic</td>
<td></td>
<td>Partial response</td>
<td>and description</td>
</tr>
</tbody>
</table>

Abbreviations: b3-bilirubin, pulse-pulmonary, SVC-superior vena cava; EBUS-TBNA-endobronchial ultrasound-guided transbronchial needle-aspiration

Conclusion: This is a series of primary thoracic sarcomas with a highlight on four extremely rare cases which bring to light their unique clinical, radiological, histopathological and immunohistochemical findings. Awareness of such entities is essential for proper diagnosis, appropriate molecular-testing and treatment.

Keywords: sarcoma, pulmonary, Primary, Immunohistochemistry
**Abstracts**

**P3.01-025 CLINICAL AND PATHOLOGICAL REAPPRAISAL OF PRIMARY LUNG CARCINOMA WITH LYMPHOEPITHELIOMA-LIKE CARCINOMA MORPHOLOGY**

Yasufumi Goda, Akihiko Yoshizawa, Toyofumi Chen-Yoshikawa, Makoto Sonobe, Hiroshi Date

Departments of Thoracic Surgery, Kyoto University, Kyoto, Japan, Kyoto/Japan

Background: Lymphoepithelioma-like carcinoma (LELC) is a rare form of lung cancer, usually encountered in Chinese patients. Similar to nasopharyngeal carcinoma which is strongly associated with Epstein-Barr virus (EBV) infection, LELC is defined as a poorly differentiated carcinoma reveals EBER-positive neoplastic cells and marked lymphocyte infiltrate by 2015 WHO classification; however, EBER-negative carcinomas showing LELC-like morphology are present and such cases might be classified as adenocarcinoma or squamous cell carcinoma based on the results of immunohistochemistry staining, such as p40 or TTF-1. Methods: We retrospectively reviewed the medical records of 5 LELC patients who underwent pulmonary resection in Kyoto University Hospital between 2005 and 2016. All five cases were primary lung tumors with histologic features of carcinoma characterized by poorly differentiated morphology admixed with heavy lymphocyte infiltrate which fit the criteria for the diagnosis of LELC as morphologic findings. Results: There were 4 men and 1 woman who ranged in age from 65 to 78 years, with a median age of 70. Three patients had lymph node metastasis and underwent surgical resection, followed by adjuvant chemotherapy. One patient died of second primary lung cancer (small cell carcinoma) but four patients were alive without tumor recurrence 4 months to 8 years and 11 months. Four patients (80%) were negative for EBV, suggesting no association between EBV and LELC in our institution study group. In immunohistochemistry staining, 4 cases were positive for p60 and one case was for TTF-1.

**Patient Data**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Smoking</th>
<th>Location</th>
<th>pStage</th>
<th>Treatment</th>
<th>EBER</th>
<th>TTF-1</th>
<th>p40</th>
<th>Outcome</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>78</td>
<td>M</td>
<td>Yes</td>
<td>RUL</td>
<td>T1aN0M0</td>
<td>Surg+adjuvant rad</td>
<td>negative</td>
<td>negative</td>
<td>positive</td>
<td>3y6m dead</td>
</tr>
<tr>
<td>2</td>
<td>68</td>
<td>M</td>
<td>Yes</td>
<td>LLL</td>
<td>T1aN2M0</td>
<td>Surg+adjuvant chemo</td>
<td>negative</td>
<td>negative</td>
<td>positive</td>
<td>8y11m alive</td>
</tr>
<tr>
<td>3</td>
<td>71</td>
<td>F</td>
<td>None</td>
<td>LLL</td>
<td>T1N1M0</td>
<td>Surg+adjuvant chemo</td>
<td>positive</td>
<td>negative</td>
<td>positive</td>
<td>6y2m alive</td>
</tr>
<tr>
<td>4</td>
<td>65</td>
<td>M</td>
<td>Yes</td>
<td>RUL</td>
<td>T1B1M0</td>
<td>Surg+adjuvant chemo</td>
<td>negative</td>
<td>negative</td>
<td>positive</td>
<td>5y1m alive</td>
</tr>
<tr>
<td>5</td>
<td>73</td>
<td>M</td>
<td>Yes</td>
<td>RUL</td>
<td>T1aN0M0</td>
<td>Surg only</td>
<td>negative</td>
<td>negative</td>
<td>positive</td>
<td>0y4m alive</td>
</tr>
</tbody>
</table>

Conclusion: Our reexamination revealed that most LELCs were negative for EBER and were classified as squamous cell carcinoma by IHC study. This results might imply that EBER is not a requisite factor in the lung carcinoma with LELC-like morphology.

Keywords: Squamous cell carcinoma, Adenocarcinoma, lymphoepithelioma-like carcinoma, EBER

**P3.01-027 3D TELOMERE NUCLEAR ORGANIZATION TO DISTINGUISH MULTIPLE SYNCHRONOUS LUNG ADENOCARCINOMA FROM METASTATIC LUNG ADENOCARCINOMA**

Nathalie Bastien, Oumar Samassékou, Michèle Orain, Sabine Mai, Philippe Joubert

Departments of Pathology, Quebec Heart and Lung Institute, Quebec/QC/Canada, 3D Signatures Inc., Winnipeg/AB/Canada, Manitoba Institute of Cell Biology, University of Manitoba, Winnipeg/AB/Canada

Background: Lung cancer is the leading cause of cancer-related mortality. Adenocarcinoma (AC) representing 50% of diagnosed lung cancer. At diagnosis, 25% of pulmonary AC present as multicentric lesions and an half are considered synchronous AC (SLA) while the remaining represents intrapulmonary metastases (MAC) from a primary lung AC. Surgical resection is the treatment of choice for SLA and the outcome of the patients is generally good. On the other hand, intrapulmonary metastases (MAC) are related lesions associated with a poor prognosis and generally not amenable to surgical therapy. There is currently no way to distinguish SLA from MAC without analyzing a surgical specimen from each lesion, which is rarely possible. It is then likely that a significant proportion of patients with multiple AC do not get the appropriate treatment. There is therefore an urgent need to develop molecular tools to classify multicentric lesions. Genomic instability is one of the drivers of metastases, and the alteration of telomeric nuclear organization (TNO) is a predictor of genomic instability and tumor progression. Our hypothesis is that the profile of TNO can discriminate SLA from MAC. Methods: We assessed the parameters defining 3D-TNO using 3D quantitative fluorescence in situ hybridization, 3D imaging and 3D-TNO analyses on formalin-fixed paraffin-embedded tissue sections from 10 patients with SLA or MAC. For each patient, we analyzed two lesions: primary and metastatic lesions for MAC and two different primary tumors for SLA. The following 3D-TNO parameters were evaluated: 1) number of telomere (telomere signals), 2) telomere length (telomere signal intensities), 3) number of telomere aggregates (telomere clusters), 4) telomere distribution within a nucleus and 5) nuclear volume. Results: Firstly, we compared 3D-TNO of cancer cells between MAC and SLA and found that four of the five parameters defining 3D-TNO showed statistical difference between the two pathological groups. Secondly, for each patient, we did pairwise comparison of parameters defining 3D-TNO between the two lesions. For the patients presenting MAC, we found that metastatic lesions had higher telomere aggregates than primary lesions. The comparison of the number of telomere aggregates did not display statistical difference between the two primary tumors from SLA.

Conclusion: This study shows that the number of telomere aggregates is a powerful discriminative parameter that can reliably distinguish patients with SLA from patients with MAC. Our results suggest that 3D-TNO signature has the potential to provide a molecular tool that can eventually be implemented in a clinical setting.

Keywords: Telomeres, lung adenocarcinoma, Multicentric lesions
P3.01-028 COMPARISON OF TOUCH IMPRINT CYTOLOGY AND SECTION HISTOPATHOLOGY IN THE DIAGNOSTIC OF THE SMALL PERIPHERAL LUNG TUMORS
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Background: There have been some reports on transbronchial biopsy (TBB) through endobronchial ultrasonography with a guide sheath (EBUS-GS) for diagnostic sampling of small-sized tumors which showing ground-glass opacity (GGO) on chest CT. However, technique such as EBUS-GS is limited in their ability to diagnose such small lung tumors. The discussion about the cytological features of small tumors with GGO in detail is necessary.

We evaluated about the association of the cytological features with the histological examination using the surgically resected specimen. 140 patients, age between 23–86 years old, who showed clinical and radiological signs of peripheral lung tumors below 3.0cm in diameter, underwent surgical resection at our institution between 2013 and 2015. Methods: Imprints or touch preparation and squash smears preparation were prepared from the unfixed, fresh sample in 140 cases. Papanicolaou’s stain was employed in all cases. To make the squash smears preparation, the slides are drawn apart away from each other, in the direction of the long axis of the slide. Tissue fragments taken from surgical specimens were fixed with 10% neutral buffered formalin and stained with hematoxylin and eosin (H&E).

Results: By histological examination (in the 140 cases), the diagnostic of lung cancer was given with the establishing of the histological type. In 110 cases (78.6%) of the cases diagnosed as adenocarcinoma, in 21 cases (15%) squamous cell carcinoma, in 4 cases (2.9%) neuroendocrine tumors, and one case each of adenosquamous carcinoma, pleomorphic carcinoma and pleomorphic sarcoma. In 84% of the 110 cases (76.3%), the result of imprint cytocological examination was adenocarcinoma. In the 110 pathological diagnosed as adenocarcinoma cases, 52 patients (47.2%) are below 2.0cm in size. Tumor stamps of small sized adenocarcinoma are characterized by moderate cellularity and are composed of atypical cells arranged in small flat sheets. The nuclei are generally round, slightly hyperchromatic with small nucleoli and granular chromatin densely are the factors of adenocarcinoma.

Keywords: trans endoscopic lung biopsy, imprint cytology, ground-glass opacity (GGO)

P3.01-029 CASES DEMONSTRATING SPREAD THROUGH AIR SPACES (STAS) REFLECTS INVASIVE GROWTH AND NOT AN ARTIFACT
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Background: STAS is defined as a pattern of tumor cell spread in the lung parenchyma beyond the edge of a lung tumor. It has been postulated that this is an ex vivo artifact due to the force of knife that STAS is clinically unimportant and it should be ignored like true artifacts. Methods: We present three cases providing evidence that STAS is not an artifact and is clinically relevant. Results: Case 1: 68F underwent wedge resection of a left upper lobe (LUL) lung adenocarcinoma. During the surgical procedure the surgeon did not cut across the tumor, but sent a separate wedge biopsy as an additional margin. The latter wedge contained an 8 mm focus of adenocarcinoma consisting almost entirely of a STAS pattern with a 1mm area of acinar growth. Case 2: 66M underwent RUL wedge resection in August 2013 for a 1.3 cm lung adenocarcinoma. The resection margin was positive with only STAS in the margin. In the absence of any clinical sign of recurrence or metastases, a completion right upper lobectomy was performed revealing three separate foci of residual adenocarcinoma including 1.5 and 1.0 mm acinar areas and a 0.5 mm focus of STAS with N1 and N2 lymph node metastases. Adjuvant chemotherapy and radiation were given. In 2014, the patient developed multiple bilateral nodules and in November underwent LUL wedge resection that showed three foci of adenocarcinoma with a STAS predominant pattern. In July 2016, the patient remains on chemotherapy with slowly growing bilateral nodules. Case 3: A 77M presented with pneumonia and bilateral ground glass opacities with focal consolidation. A biopsy, originally interpreted as benign, showed diffuse involvement by adenocarcinoma with a STAS predominant pattern. The morphology does not explain the consolidation seen on CT indicating the surgeon did not cut across the main tumor area. Conclusion: We present three cases which provide evidence that STAS is not an artifact that should be ignored. In two cases the extensive STAS predominant pattern was not a knife cutting artifact because the main tumor was not cut either by the surgeon or pathologist. In the third case, STAS was the only pattern of tumor identified at a wedge resection margin. If this had been ignored, the residual and metastatic tumor would not have been identified delaying introduction of chemotherapy. These findings support the concept that STAS is a clinically important invasive pattern and not an artifact.

Keywords: Spread Through Air Spaces, Invasive pattern, Artifact, Cases

P3.01-030 CORRELATION OF PREOPERATIVE CT CHARACTERISTICS AND HISTOLOGIC PATTERNS OF PULMONARY ADENOCARCINOMA
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Background: Comparison of radiographic parameters and histologic sub-types of lung adenocarcinomas (ADCs) proposed by the IASLC/ATS/ERS in 2011 may help to direct surgical procedures and evaluate prognosis. To analyze the relationship between them, we conducted our study. Methods: The architectural patterns of 197 completely resected lung ADCs were analyzed in 5% increments, and classified and graded according to their predominant patterns. Preoperative CT imaging characteristics, including lesion site, diameter, shape, margins, attenuation, cavitlation, et al, were also collected. Results: Low-grade group (including lepidic predominant ADC, LPA) was more likely linked with vague boundary, irregular shape, vascular clusters and GGO or sub-solid nodules (SSN), while high-grade group (including solid predominant ADC, SPA and micro-papillary predominant ADC, MPA) were vice versa (p-values were 0.003, 0.037, 0.037, 0.011, respectively). More proportion of lepidic growth pattern were detected in GGOs or SSNs (p<0.001), and in those lesions characterized by the following CT features, such as vague boundary, non-lobulated margins, cavitlation, irregular shape and vascular clusters (p<0.040, 0.009, 0.040, respectively). The proportion of lepidic growth pattern was more likely linked with vague boundary, irregular shape, vascular clusters and GGO or sub-solid nodules were associated with solid lesions on CT (p<0.006, 0.020, respectively). More proportion of Solid growth pattern were detected in spherical tumors (p=0.016). Conclusion: We conclude that CT imaging characteristics are associated with histo-morphological patterns of ADC to some extent. It may offer some clues for the diagnosis of ADC and predicting its survivals as well.

Keywords: radiology, pulmonary adenocarcinoma, histology, subtyping
Abstracts

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Background: Incomplete retrieval of intrapulmonary lymph node and missed nodal metastasis are associated with worse-than-expected survival after (NSCLC) resection. We tested the nodal yield from a novel gross dissection method. Methods: multi-institutional prospective cohort study of intrapulmonary (stations 11-14) lymph node yield from lobectomy/ greater NSCLC resection specimens from 11 US hospitals from 2009-2016. A novel gross dissection protocol was used in 2 hospital pathology departments from June 2012 onwards. Intrapulmonary lymph node yields from all lobectomy or greater resections before and after the new protocol in the intervention hospitals were compared to yields from 9 non-intervention hospitals over the same time-span, using Wilcoxon-Mann-Whitney. From February 2015, some randomly selected re-dissected remnant lung specimens in the intervention hospitals were re-dissected for inadvertently discarded lymph nodes as a quality control measure. Results: Intrapulmonary lymph node yields in the 2 groups of hospitals was similar at baseline, followed by a significant increase in the intervention hospitals with the novel dissection protocol (Table 1). Subsequently, in 112 specimens re-dissected for independent quality control after application of the novel dissection protocol, discarded lymph node yields were found in 38/112 (34%) historically down from 56/112 (50%) historically; discarded lymph node yields with metastasis in 6/112 (5%), down from 29/112 historically; and missed N1 nodal metastasis was found in 1 of 67 (1.5%) pN0 patients, down from 12% historically. The median number of missed intrapulmonary lymph node yields was 0 (down from 6 historically), the mean (standard deviation) was 0.89 (2.58). The gross dissection protocol required a median of 15 minutes (range 10–24).

Conclusion: A novel gross dissection protocol significantly improves the thoroughness of intrapulmonary lymph node retrieval and can be successfully implemented in community-level pathology departments, providing a pathway for quality improvement in pathologic nodal staging of resected NSCLC.

Keywords: Quality of care, Pathologic staging, lymph nodes, lung cancer surgery


P3.01-032 PELP1 EXPRESSION IN MOLECULARLY CLASSIFIED LUNG ADENOCARCINOMAS

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Background: Proline-, glutamic acid-, and leucine-rich protein 1 (PELP1) is a scaffolding protein which functions as a coregulator of several transcription factors and nuclear receptors. It has a histone-binding domain and plays essential roles in several pathways including hormonal signaling. PELP1 is a coregulator of estrogen receptor (ER) and has been shown to be deregulated, contributing to therapy resistance and is a prognostic biomarker in breast cancer survival, as well as in other hormone-dependent cancers. Estrogens are also known to enhance lung tumorigenesis by estrogen receptor pathway.

In this study, we investigated the expression of PELP1 in molecularly classified lung adenocarcinomas, specifically those with known EGFR and KRAS mutations. Methods: Tissue microarray (TMA) was created using 0.6 mm tissue cores in triplicates from 62 resected lung adenocarcinoma cases (26 with EGFR mutation and 36 with KRAS mutation). PELP1 antibody (Clone EPR15212, ABACAM) immunostaining was performed after heat induced epitope permeation and the progression into macrometastases. As a result, the mitotic index of cancer cells in each case was significantly lower than in PT and LN-Mac (p<0.05). Conclusion: In lung squamous cell carcinoma, drastic microenvironmental changes (e.g., growth factor receptor expression and proliferative capacity of cancer cells and structural changes in stromal cells) occur during both the process of lymphatic permeation and the progression into macrometastases.

Keywords: lymph node metastasis, Lung Squamous cell carcinoma, micrometastasis, cancer microenvironment


P3.01-034 MIGRATION AND EPITHELIAL TO MESENCHYMAL TRANSITION OF LUNG CANCER CAN BE TARGETED VIA TRANSLATION INITIATION FACTORS EIF4E AND EIF4GI

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Background: Non small cell lung cancer (NSCLC) metastasis remains a major cause for patient mortality marking the underlying molecular mechanisms as important therapeutic targets. The progression of cancers from primary tumors and scored similarly. Results: In our study, 61 cases had evaluable tissue cores with tumor. Positive PELP1 expression was noted in 14/25 (56%) EGFR mutated and 30/36 (83%) in KRAS mutated lung adenocarcinomas (p<0.05). From the EGFR-mutated group, 4/25 (16%) reveal weak (+) and focal staining for ER while one case revealed strong ER staining. From the KRAS-mutated group, 2/36 (5%) cases revealed weak (+) staining for ER. All these cases with ER positivity (7/6; 11.5%) were also positive for PELP1. Conclusion: Our study has demonstrated that apart from PELP1 expression in ER positive lung adenocarcinomas, it can also be seen in estrogen receptor negative molecularly classified lung adenocarcinomas. It is more often seen in KRAS mutated lung adenocarcinomas. Estrogen receptor independent PELP1 expression in lung adenocarcinoma suggests presence of alternate pathways for tumorigenesis or tumor progression, which needs further investigation; especially in KRAS mutated lung adenocarcinomas. References: 1. Slowokowicz BK, Gatedick B, Dzyskiec W et al. Increased expression of prlone-, glutamic acid- and leucine-rich protein PELP1 in non-small cell lung cancer. Biomed Pharmacother 73:97101; 2015. 2. Saredy GV, Vadlamudi RK. PELP1: Structure, biological function and clinical significance. Gene. 585(1):128-34; 2016.

Keywords: PELP1, ER, Lung Adenocarcinoma
to invasive and metastatic stages accounts for the overwhelming majority of NSCLC patients deaths. Understanding the molecular events which promote metastasis is thus critical in the clinic. Deregulation of protein synthesis is integral to the malignant phenotype and translational control is emerging as an important factor in tumorigenesis. Indeed, over-expression of translation initiation factors eIF4E and eIF4G in NSCLC was associated with patients’ poor survival. Thus, in this study we aimed to assess the direct role of eIF4E and eIF4G in NSCLC and their effect on migration and metastasis formation. Methods: eIF4E/eIF4G knockdown (KD) in NSCLC cell lines (H1299, H460) was achieved by siRNA. Following transfection the cells were tested for changes in eIF4E/eIF4GIs’ targets (SMAD5, NFKb, cMYC, HIF1α), migration (scratch) and pro/anti Epithelial-Mesenchymal Transition (EMT) markers (N-Cadherin, Slug, ZEB1, E-Cadherin, Claudin, ZO-1, microRNA). Importance of eIF4E and eIF4G KD to NSCLC phenotype was further corroborated with the inhibitors ribavarin and 4EGI-1. Lastly, we tested for changes in essential microRNA implicated in NSCLC cell migration and EMT. Results: Downregulation of eIF4E/eIF4G significantly decreased their established targets (20-35%), 48h, p<0.05 indicating compromised activity. Diminished NSCLC cells’ migration upon eIF4E/eIF4G KD was also witnessed (65-82%), 48h, p<0.05). Moreover, we demonstrated reduced levels of EMT inducers together with elevated levels of EMT suppressors (40-90%), 48h, p<0.05). Finally, we showed that eIF4E/eIF4G KD affected miRNAs critically involved in migration and EMT processes. Conclusion: Our study shows that targeting eIF4E/eIF4G reduces migration and EMT, both essential for metastasis, thereby underscoring the role of translation initiation in NSCLC metastatic tumor formation. Understanding the molecular events which promote metastasis and improving the means of foretelling their development is a major goal of current clinical research.

Keywords: hepatocyte growth factor, α7 nicotinic acetylcholine receptor, phosphoinositide kinase-3, lung cancer, migration

Conclusion: These results indicate that nicotine, when alone, does not have a promigratory function, but instead enhances responsiveness to the promigratory stimulus emitted by HGF. This study provides an insight into the mechanism of tumor promotion by demonstrating that nicotine and α7NACHr act in synergy with the HGF induced PI3K/Akt signaling pathway, increasing the sensitivity of lung cancer cells to HGF, and thereby promoting cell migration, a vital step in invasion and metastasis.

Keywords: hepatocyte growth factor, α7 nicotinic acetylcholine receptor, phosphoinositide kinase-3, lung cancer, migration
target genes, termed as hypoxia response element (HRE). However, a genetic variant of HIF was not fully understood. Previously, we reported that HIF1A polymorphism associated with TP53 status in lung cancer patients, and transcription variants of the HIF–variants in A549 lung cancer cells was significantly greater than that of the wild type, especially in cells containing a mutant type of p53. We also found that one of HIF2A (EPAS1) polymorphism significantly associated with poorer prognosis of lung cancer patients, and the nucleotide substitution might affect HIF-2 expression through transcription and translation in vitro. Methods: In this study, we tried to clarify a role of genetic variations of HIF3A gene, and started evaluations of six polymorphisms located in HIF3A loci (rs3764609, rs3764610, rs3764611, rs375220, rs3810302, rs3826976) in 83 Japanese lung cancer patients as a pilot study. Results: We performed sequence analysis of genomic DNA and use a direct identification of polymorphisms by direct sequencing. Genotype distributions of each SNP showed good agreements with the Hardy-Weinberg equilibrium. We found the rs3810302 have different genotype distribution compare healthy Japanese data base (HapMap, p=0.01). Then, some loci of HIF3A showed significant associated with clinicopathological of lung cancer patients (stage, cancer differentiation, histology, etc). Conclusion Our preliminary study suggested that some of HIF3A polymorphisms showed significantly important associations with lung cancer clinicopathological. More studies were further required to focus on its relationship.

Keywords: lung cancer, HIF3A, Hypoxia, polymorphism

POSTER SESSION 3 – P3.01: BIOLOGY/PATHOLOGY
FUNCTIONAL BIOLOGY IN LUNG CANCER
WEDNESDAY, DECEMBER 7, 2016

P3.01-038 STAT3 AND SRC-YAP1 INHIBITION RESULTS IN GREATERTICUMUMAB SUSCEPTIBILITY IN LUNG SQUMOUS CELL CARCINOMA
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Background: The anti-EGFR monoclonal antibody (mAb), necitumumab, has been recently approved in combination with chemotherapy, as 1st-line treatment for advanced lung squamous cell carcinoma (LSCC) patients, but with minimal survival benefit. Evidence continues to accumulate that signal transducer and activator of transcription 3 (STAT3) is a promising molecular target for cancer therapies. STAT3 is activated by tyrosine phosphorylation in response to EGF and interleukin-6 (IL-6). In addition to STAT3, IL-6 activates the Src family kinases, and subsequently YES-associated protein 1 (YAP1). STAT3 and Src-YAP1 activation contributes to EGFR inhibitor resistance and concomitant targeting of EGFR and STAT3-3rc may represent an effective treatment strategy for LSCC. Methods: RNA was isolated from six LSCC cell lines and the mRNA expression analysis of EGFR, STAT3, Src and YAP1 was performed by TaqMan based qRT-PCR. Cell viability was assessed by MTT assay, Scratch-wound healing assay, Transwell migration and invasion assay were conducted to study the proliferation, migration and invasion abilities of lung cancer cells independently. The shRNA and overexpression plasmids of JAK2 were conducted. Results: JAK2 is up-regulated in lung cancer tissues when compared with their adjacent non-tumor tissues, and was associated with lymph node metastasis. Downregulation of JAK2 inhibits the proliferation, migration and invasion abilities of lung cancer cells. Moreover, overexpression of JAK2 induced the proliferation, migration and invasion abilities of lung cancer cells. Conclusion: These findings demonstrate that JAK2, whose expression is up-regulated in lung cancer, may participate in lung cancer progression by regulating cancer cell proliferation, migration and invasion.

Keywords: lung cancer, JAK2, proliferation, Migration

POSTER SESSION 3 – P3.01: BIOLOGY/PATHOLOGY
FUNCTIONAL BIOLOGY IN LUNG CANCER
WEDNESDAY, DECEMBER 7, 2016

P3.01-040 DIFFERENCE OF GRAPHENE OXIDE-INDUCED AUTOPHAGY BETWEEN ADENOCARCINOMA AND MACROPHAGE CELL LINE
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Background: Chemotherapy against nonsmall cell lung cancers is remarkably progressing. Nanomaterials are searched for this therapy. Graphene oxide is also suggested as one of promising therapeutic materials. Graphene is an allotrope of carbon with honeycomb structure. It may show the diverse biologic effects from minimal to highly toxic effect according to the cell type. The goal of this study was to define the differential cell death mechanism of graphene oxide on lung adenocarcinoma cells and macrophages with different autophagy. Methods: A549 cells and Raw264.7 cells were cultured in Dulbecco’s modified eagle’s medium with 10 % fetal bovine serum and treated with graphene oxide(GO). GO was treated to the cells in the range of 5 ~ 200 μg/ml for 24 and 48 hours. Cell survival was examined with light microscopy and MTT assay. Protein expression was checked by Western blots for LC3A/B, p62/SQSTM1, mTOR, Beclin-1 and PDI (monocyte/macrophage-specific transcription factor). Results: Higher concentrations of graphene oxide induced increasing cellular death with different intensity between A549 and Raw264.7 cells. LC3B-1 to LC conversion (autophagy) was increased by GO in A549 cells and decreased in Raw264.7 cells. Expression of NBR1 and Beclin-2 showed same directional change in both cell types. The mammalian TOR was also decreased in A549 cells. GO (monocyte/macrophage-specific transcription factor) was decreased in Raw264.7 cells. Beclin-1 and GAPDH was not affected by GO in both cells. Conclusion: This study showed the opposite response in autophagy in A549 cells and Raw264.7 cells. Although the precise mechanisms are mandatory to be defined, graphene may be used for selective

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targeting against lung adenocarcinoma with preserving immune function.

P3.01-041 ANTI-CANCER EFFECT OF HYPEROXIA ON HUMAN LUNG CANCER CELLS THROUGH OXIDATIVE STRESS MEDIATED ERK SIGNALING
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Background: Abnormal increases in reactive oxygen species (ROS) in cancer cells serve as a target for tumor-selective killing. Also, several experimental and clinical trials studied the effect of the hyperoxia condition by difference of response between normal cells and cancer cells. In this study, the hypothesis tested was that normobaric high oxygen concentration would have anti-cancer effects such as inducing apoptosis on human lung cancer cell line. Methods: Human bronchial epithelial cells (Beas-2b) and human alveolar adenocarcinoma cells (A549) were exposed with hyperoxia condition in a time-dependent manner. Changes in the cell morphology, viability and protein expressions such as p53 and ERK were examined after the exposure of hyperoxia (90% O2). In addition, to investigate whether hyperoxia condition affects the production of ROS and cell cycle regulation, cells were analyzed by a flow cytometry. Results: Exposure to the hyperoxia caused morphologic changes such as atypical nuclei and numerous mitotic figures which inhibited the cell viability in a time-dependent manner in A549 (p <0.01). In addition, the colony formation was suppressed selectively in A549 exposed to hyperoxia. Although not statistically significant, A549 exposed to hyperoxia showed increases in the ROS levels compared with Beas-2b. Also, the hyperoxia condition caused a progression delay in the G2/M cell cycle significantly in A549 (p <0.01). In hyperoxia exposed A549 cells, the phosphorylation of ERK 1/2 (p-ERK 1/2) was reduced while the phosphorylation of p53 was increased. Conclusion: This study showed that hyperoxia may have anti-cancer effect by decreasing cell viability and the colony forming ability. ROS generation by hyperoxia may cause to suppress the p-ERK, it related with the activation of p53 and G2/M cell cycle arrest. In conclusion, our data suggests that the anti-cancer effect of hyperoxia may relate to the ROS through oxidative stress mediated ERK signaling and cell arrest.

Keywords: hyperoxia, oxidative stress, lung cancer

P3.01-042 LUNG CANCER CELLS CAN STIMULATE FUNCTIONAL AND GENOTYPIC MODIFICATIONS IN NORMAL BRONCHIAL EPITHELIAL CELLS
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Background: Normal lung epithelium cells may act in concert with tumour cells, given that bystander effects may exist between the two. This interaction may lead to inappropriate activation of pro-angiogenic signalling pathways, which may result in high mutational load and tumour heterogeneity. The aim of this project is to evaluate the effects of non-small cell lung cancer (NSCLC) cells on an immortalised normal bronchial epithelial cell line. Methods: A normal bronchial epithelial cell line (HBE4C) was exposed to A549 (adenocarcinoma), H460 (large cell carcinoma) and SK-MES-1 (squamous cell carcinoma) NSCLC cell lines in a trans-well co-culture system. Cellular characteristics were examined using a CyteII Cell Imaging System (cell number, viability, apoptosis, cell cycle). The gene expression profile was also determined in terms of inflammatory mediators, stem cell markers (RT-PCR) and miRNA profiling (Nanostring). The proliferative effect of NSCLC cancer cell lines was also examined (BrdU ELISA) on the HBE4C cell line. Results: A number of functional and gene modifications were observed in the HBE4C cell line after seven days of co-culture. While patterns were similar amongst all NSCLC subtypes, SK-MES-1 elicited the most significant effects in terms of cell number, viability, cell cycle progression and proliferative potential of isolated cancer exosome fraction. Promotion of both inflammatory mediators and stem cell marker expression was evident at the mRNA level. There was no apparent consensus between NSCLC subtypes and miRNA expression, as exposure to each cell line resulted in distinct profiles of miRNAs in HBE4C cells. Bioinformatic analysis of miRNA target genes, demonstrated that pathways such as p53, MAPK, VEGF, TLR and Wnt were amongst those altered. Conclusion: Cancer cells may promote significant genotypic and phenotypic alterations within the normal lung epithelium through multiple mechanisms. These modifications may, in part, contribute to the heterogeneity of lung cancer tumours and influence response to both chemotherapeutics and targeted agents.

Keywords: HBE4C, non-small cell lung cancer, miRNA, inflammation

P3.01-044 INHIBITION OF ORNITHINE DECARBOXYLASE FACILITATES PEGYLATED ARGININE TREATMENT IN LUNG ADENOCARCINOMA XENOGRAFT MODELS
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Background: Arginine depletion has shown promising anticancer effects among arginase autotrophic cancers that are deficient in argininosuccinate synthetase (ASS) and/or ornithine transcarbamylase (OTC). Pegylated arginine (PEG-BCT-100 (rhArgpegs5000)) works as an arginine depletor by competing arginine and ornithine. However, accumulated ornithine can be channeled via ornithine decarboxylase (ODC) to produce polyamines that are known to promote tumor growth. We postulate that ODC inhibition could rescue anticancer effects of BCT-100 in lung adenocarcinoma. Methods: A panel of 7 lung adenocarcinoma cell lines (H22, H358, HCC287, H1650, H1975, HCC2935 and HCC4006) was used to study the in vivo effect of BCT-100 by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. The in vivo effect of BCT-100 was studied using 5 nude mice xenograft models lines (H358, HCC287, H1650, H1975 and HCC4006). Protein expression and arginine concentration were investigated by Western blot and ELISA respectively. TUNEL assay was performed to identify apoptosis. Results: BCT-100 could not inhibit tumor growth in HCC4006 xenograft model, while paradoxical growth stimulation was observed in H358, HCC287, H1650 and H1975 xenograft models. Upon BCT-100 treatment, ODC was induced in two solid tumor xenograft models (H1650 and H1975), while unaltered in cystic tumor xenograft models (H358 and HCC287) and the remaining solid tumor (HCC4006) xenograft model. In both H1650 and H1975 xenografts, combined BCT-100 and α-Difluoromethylornithine (DFMO, an ODC inhibitor) significantly suppressed tumor growth compared with control or single arm treatments with median survival doubled compared with control group. Apoptosis was activated in combination arm in both xenograft models. In HCC4006 xenograft model, the tumor suppression effect of BCT-100 arm and DFMO/BCT-100 arm was similar. Apoptosis was noted in DFMO, BCT-100 and DFMO/BCT-10 arms. Conclusion: Inhibition of ODC by DFMO is essential in BCT-100 (pegylated arginine) treatment in lung adenocarcinoma.

Keywords: pegylated arginine, Difluoromethylornithine, lung adenocarcinoma, apoptosis

P3.01-043 SPLICING VARIANT OF ESTROGEN RECEPTOR ALPHA IS ASSOCIATED WITH PATHOLOGICAL INVASIVENESS IN SMOKING INDEPENDENT LUNG CANCER
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Background: Smoking independent lung cancers are consisted mainly of female patients, but the molecular background of this epidemiological feature other than EGFR mutation is still vague. Several studies have reported the correlation between female hormone related factors and the biological features of lung cancer. The aim of this study is to clarify the correlation between female hormone related factors and the pathological invasiveness of smoking independent lung cancer.

Methods: We examined the pathological invasiveness of smoking independent lung cancer by estrogen receptor alpha (ERα) expression and its alternative splicing. In this study, we analyzed 103 cases of pathological smoking independent lung cancer. We sequenced the exons 1–12 of ERα gene and analyzed the relative expression of ERα in cancerous and non-tumor tissues.

Results: We found that the alternative splicing of ERα at intron 6 was associated with the pathological invasiveness of smoking independent lung cancer. The expression of the alternative splicing variant was significantly lower in the pathological smoking independent lung cancer with high pathological invasiveness.

Conclusion: The alternative splicing variant of ERα is associated with the pathological invasiveness of smoking independent lung cancer.
prognosis of lung cancer, but the results are still inconsistent. We focused on the expression of aromatase, estrogen receptor alpha (ER alpha), and estrogen receptor beta (ER beta) to investigate the carcinogenesis of smoking-independent lung cancer. Methods: Immuno histochemistry staining (IHC) of aromatase, ER alpha, and ER beta was performed against formalin-fixed tissues from 38 never-smoking patients who underwent complete surgical resection between 2012 and 2013. Among them, adequate RNA of the tumor and adjacent normal lung were extracted from deep frozen tissues of 31 patients. Considering the IHC results, quantitative RT-PCR (qRT-PCR) was performed to measure the expression level of aromatase and 3 different exons of ER alpha (exon5-S, exon6, and exon7) which composes the ligand binding motif using the Taqman® method. Results: Extra-nuclear expression of ER alpha with IHC showed significant correlation with pathological invasiveness, statistically, qRT-PCR results showed decreased expression of ER alpha exon 7 in invasive tumor tissues, compared with their adjacent normal tissues. This is consistent with previous in vitro results indicating that extra-nuclear ER alpha were exon7 splicing variants. There was no difference of ER alpha exon7 expression between normal and tumor tissues in non-invasive lung cancer tissues. When considering EGFR mutation status, EGFR wild type lung cancers showed lower ER alpha exon7 expressions compared with EGFR mutated lung cancers. Conclusion: Extra-nuclear expression of ER alpha, which may represent exon7 splicing variants of ER alpha, correlates with pathological invasiveness in smoking independent lung cancer. It may also have a part in carcinogenesis of EGFR wild type lung cancer.

Keywords: never smoker, lung cancer, Estrogen receptor alpha

P3.01-045 SEX DIFFERENCES IN CXCR4-DEPENDENT MOTILITY OF NSCLC CELLS
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Background: The overwhelming majority of deaths due to lung cancer result from metastatic progression of the disease. Cytokines, a group of proteins involved in cell signaling, play an important role in activating the migratory and invasive capabilities of cancer cells, and studies have implicated thestromal-derived factor 1 (SDF-1/CXCL12)-CXCR4 cytokine signaling axis in the progression of several metastatic cancers, including that of the lung. Our previous investigations have shown that survival outcomes of female stage IV non-small cell lung cancer (NSCLC) patients with high CXCR4 levels are significantly worse compared to those of patients with low CXCR4, whereas male patients show no difference in survival. Studies in NSCLC cell lines have observed a link between CXCR4/SDF-1 and estrogen receptor (ER) function, as well as proliferation in response to treatment with estradiol (an estrogen) specifically in female cell lines. These previous results form the rationale for this project, which explores potential sex differences in the motility of NSCLC cell lines in response to cytokine and estrogen stimulation. Methods: Western blotting and PCR methodologies were used to assess the downstream activation of CXCR4 and estrogen receptor signaling as a means to confirm their activity in the cell lines studied. The migratory potential of NSCLC cells was measured using wound healing migration assays (scratch tests). Cells were incubated in phenol red-free RPMI 1640 media with or without the reagents of interest (SDF-1, beta-estradiol, estrogen and CXCR4 antagonists, among others) and the migration of cells into the wound was quantified to approximate the metastatic behavior of NSCLC cells in the presence or absence of the aforementioned stimuli. Results: All NSCLC cell lines studied showed high levels of CXCR4, but ER expression varied within our cell line panel, largely by gender of origin. Our preliminary data show a tentative but observable difference in how male and female NSCLC cells respond to both stimulation and inhibition of the CXCR4 axis. In addition, estrogen and SDF-1 co-stimulation induces a greater increase in cell motility of female NSCLC cells. Conclusion: The results observed may suggest a possible mechanism, through interactions between CXCR4 and estrogen receptor signaling pathways, to explain the extreme survival differences between male and female stage IV NSCLC patients with high CXCR4 expression.

Keywords: metastasis, CXCR4, Estrogen, NSCLC

P3.01-046 KLOTHO REGULATES EPITHELIAL-MESENCHYMAL
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Background: Klotho gene was known as one of the anti-aging gene. We previously reported that the expression of the Klotho gene was an important postoperative prognosticator for lung large cell neuroendocrine carcinoma and lung small cell carcinoma. Recently, it has been shown that the Klotho gene suppresses epithelial-mesenchymal transition (EMT). In this study, we examined the association between the expression of Klotho and the regulation of EMT in lung squamous cell carcinoma. Methods: We examined the expression of Klotho in patients with lung squamous cell carcinoma, who received surgical resection or photodynamic therapy, by immunohistochemical analysis. In order to elucidate the association between the expression of Klotho and expression of EMT related protein, such as E-cadherin, N-cadherin, Vimentin and Snail, we transfected GFP-Klotho plasmid DNA into human squamous lung cancer cell line SQS. Twenty four hours later, we sorted GFP-positive cells by flow cytometry using FACSCantoll (BD Biosciences, CA, USA), and then we examined the protein levels by Western blot analysis. Results: By immunohistochemical analysis, Klotho expression was observed in not only normal bronchial epithelial cells but also centrally located early lung cancers, which were all carcinoma in situ and treated by PDT. However, in lung cancer patients with invasive and or advanced squamous cell carcinoma who received surgical resection completely, Klotho expression was observed in only 4 patients (13%). In SQS cells transiently overexpressing GFP-Klotho, the expression of N-cadherin, which is a marker of mesenchymal state, was completely inhibited compared with the SQS cells transfected with GFP vector. Overexpression of Klotho affected the regulation of neither other mesenchymal markers such as Vimentin and Snail nor epithelial marker, E-cadherin. Conclusion: We conclude that the expression of Klotho was related to the cancer invasiveness and Klotho inhibited the expression of N-cadherin, and regulates the EMT in lung cancer. Klotho may play an important role in cancer treatment and molecular-targeted therapy.

Keywords: lung cancer, Squamous cell carcinoma, Klotho, EMT

P3.01-047 FOOD FOR THOUGHT: SHOULD WE ANALYZE A CANCER CELL AS A BIOLOGICAL MECHANISM OR AS A BIOLOGICAL COMPUTER?
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Background: We are presenting our view of the similarities between the human/cancer cell and a theoretical biological computer. We would like to challenge the actual view on the cancer cell actions as random processes. Our hypothesis is that the cancer cell is behaving as a biological computer with programmed actions and that should have an impact on the way we are dealing with cancer. Methods: Section not applicable Results: We suggest that the cancer cell should be analyzed as a digital system. Normal versus erratic cell function could be compared to normal versus erroneous computer program. In that case, we should try to find the program that has gone awry and modify it to stop the cancer instead of trying to block the peripheral effects of that program which is leading to sub-optimal results. If the cell has a program code, it could not be in the genome that we have decoded. In the digital parallel of the human/cancer cell is biological computer consisting of the input units in the cell membrane, analog/digital converters in the cytoplasm and digital processing unit in the nucleus. The result of that program is then converted through digital/analog converters (mRNA), activating different processes in the cytoplasm or leading to the synthesis of new molecules. Blocking the effectors pathways can lead to temporary slowing down of the tumor until the program code finds the solution for that obstacle. In our model, the permanent termination can be achieved only by blocking the program code. To do so, we have to find which part of the program code is active in cancer cell and with methods of reverse engineering find the solution to correct/depth/stop that program from execution. Conclusion: In our opinion the shift in paradigm of cancer cell from a biological mechanism to a biological computer should be made. Tailoring research based on that premise with the tools used in analyzing the unknown program code and modified to a biological system could lead to better understanding and treatment of cancer.

Keywords: Cancer biology, Non-coding DNA, Cancer genomic
P3.01-048 CIGARETTE SMOKING IS ASSOCIATED WITH EPITHELIO-MESENCHYMAL TRANSITION IN HUMAN ADENOCARCINOMA

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Background: Cigarette smoking (CS) is well known to cause lung cancer. In addition to the mechanisms of tumorigenesis of lung cancer with CS, a lot of evidences are currently accumulating that CS induces epithelio-mesenchymal transition (EMT) in tumor cells. The correlation of CS with the malignant progression in human lung adenocarcinoma. Methods: Clinical samples were obtained from the 239 cases of resected lung adenocarcinoma which were consecutively operated from January 2001 to December 2007 in our institution. Pathological stage distribution of the cases by TNM classification (WHO, 7th edition) was as follows: I: 118, II: 71, IIA: 22, IIB: 4, IIIA: 3, IIB: 3. Smoking history was taken from all the patients, then their smoking status was classified into 3 groups according to the Brinkman Index (Non, n=109; Light; n=400; Heavy; n=393 from 1 to 400, n=101). The samples were immunostained against E-cadherin and Vimentin using tissue microarrays of resected specimens to assess the activation level of EMT. Then, we classified into 3 groups: the group 'P', E-/V+, 'full' EMT; the group 'F', E-/V- or E+/V+, 'partial' EMT. The groups: the group 'N', E-cadherin(E+) and Vimentin(V-), "null" EMT activation; the group 'I', E-/V- and Vimentin(V+), 'intermediate' EMT. The numbers of the groups P/F/N were 38/93/190, respectively. Further, DNA samples were extracted from frozen surgical samples and the mutations for the hot-spot exons of EGFR, K-ras, and p53 were detected by SSP or direct sequencing methods. The differences of survival duration, pathological invasive factors, DNA mutations and EMT activation level were statistically analyzed among smoking groups. Results: Significant difference was found in 5-year survival rate among 3 smoking groups: Non, 89.1%; Light, 89.5%; Heavy, 61.7%. Smoking status was significantly associated with EMT activation, DNA mutation status, local invasive factors, and lymph-node metastasis. In the tumors harboring either wild-type K-ras or wild-type p53, heavy smoking was associated with active DNA damage (p<0.002), respectively, whereas no correlation with regard to EMT status. Conclusion: Smoking amount had a significant association with EMT activation level and malignant progression of human adenocarcinoma. Heavy smoking was related with EMT activation of the tumors with wild-type K-ras or p53.

Keywords: lung adenocarcinoma, EMT smoking

P3.01-050 ISOLATION AND CHARACTERIZATION OF LYMPHATIC ENDOTHELIAL CELLS FROM NEOPLASTIC AND NORMAL HUMAN LUNG

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Background: Cell culture models may be crucial to study lung microvascular endothelium and its role in cancer progression and treatment. In addition, a high heterogeneity among endothelial cells from various disease circumstances may have been demonstrated, with greater difference on the lymphatic circulatory system. Organ-specific endothelial cells are essential to elucidate signalling pathways involved in the pathogenetic mechanisms of neoplastic lung diseases and to provide novel approaches to reach the goal of a true personalized therapy. The aim of the present study was to isolate and characterize lymphatic endothelial cells from neoplastic and healthy human lung. Methods: A simple and unexpensive method, requiring minimal equipment and accessories was utilized to harvest, isolate and expand lymphatic endothelial cells from human lung (Lu-LEC). Specifically, samples from lung cancer (T) and spared distal lung (D) of 46 patients undergoing lobectomy or pneumonectomy for NSCLC, were processed. To obtain a pure population of Lu-LEC, a two-step purification tool based on sorting with monoclonal antibody to CD31 and podoplanin coated paramagnetic beads was employed. Immunohistochemical analysis on harvested pulmonary tissues was performed to assess the presence or absence of neoplastic cells and to define the specific lymphatic vasculature. Results: The purity of cultured endothelial cells was ascertained by morphologic criteria including TEM analysis, immunocytochemistry, flow cytometry and functional assays. T and D-Lu-LECs were positive for CD31. Moreover, to define the lymphatic phenotype, we examined the specific markers podoplanin, LVEF1 and Prov1. No significant immunophenotypic differences between D and T Lu-LEC were detected by FACS. Although T Lu-LEC were larger than D Lu-LEC, morphologic features as cytoplasmatic microvesicles, Weibel-Palade Bodies and aggregate of parallel intermediate filaments were equally observed. Lu-LEC and D-Lu-LEC were characterized in vitro for their ability to express several receptor tyrosine kinases (RTKs) implicated in cell survival and proliferation and in the development and progression of cancer. Cultured lymphatic endothelial cells variably expressed VEGFR2, VEGFR3, PDGFRbeta, c-met, and IGFR according to D or T origin. Moreover, VEGFR1 and PDGFRbeta were present in a lower proportion of T and D Lu-LEC. Matrigel assay documented that T Lu-LEC more efficiently organized in tubular structures at early time point when compared to D counterpart. Conversely, wound healing assay revealed that D Lu-LEC had a superior migratory ability. Conclusion: Primary lines of LECS from the human lung have been consistently obtained

P3.01-049 ELF3 OVEREXPRESSION LEADS TO ONCOGENIC REPROGRAMMING OF PROTEIN INTERACTIONS EXPOSING THERAPEUTICALLY ACTIONABLE TARGETS

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and may represent an important tool to study NSCLC microenvironment, lymphangiogenisis and anti-cancer therapy.

Keywords: tyrosine kinase receptors, lymphangiogenisis, NSCLC, tumor microenvironment

POSTER SESSION 3 - P3.01: BIOLOGY/PATHOLOGY
FUNCTIONAL BIOLOGY IN LUNG CANCER
WEDNESDAY, DECEMBER 7, 2016

P3.01-051 ANALYSIS OF MOLECULAR ABERRATIONS ASSOCIATED WITH COPD IN PATIENTS WITH LUNG CANCER
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Background: Chronic obstructive pulmonary disease (COPD) is serious lung disease that is often associated with development of lung cancer. It is well known that both diseases share many common risk factors, most prominently smoking. Much less is known about molecular link between these two pathologies. How to predict which COPD patients will develop lung cancer? Can COPD drugs reduce or increase lung cancer risk? Methods: To answer these questions we analyzed molecular data from tumour and normal tissue samples obtained from 72 lung cancer patients, comprising methylation, copy number aberrations, gene expression and microRNA expression data acquired from each sample. Various matching spriometric parameters, were used as indicator of severity of the airflow limitation in patients with COPD and were evaluated as potential prognostic indicators with respect to survival. We studied molecular aberrations to identify those that correlate with these parameters or differ between COPD and non-COPD patients. Using data from Broad Institute’s Connectivity Map (CMAp), we analyzed gene expression effects of various pharmacological compounds, to identify potential benefits/hazards in administration of various drugs (and their combinations) typically used for treatment of COPD and/or lung cancer, with respect to prognosis of patients with COPD vs. those without COPD. Results: We identified group of 619 genes and 20 microRNAs whose expression is significantly associated with patient’s COPD status (and severity of the disease). COPD-associated genes significantly enrich pathways related to G protein coupled receptors signalling, Rho GT Pases signalling and several cancer-related pathways. We found that subset of these genes constitute prognostic signature that was subsequently validated using independent publicly available dataset (HR = 2.66, p < 0.01, N = 204, GSE33120). We have also shown that alternative signature with similar prognostic power can also be constituted by COPD-associated microRNAs (HR = 2.07, p < 0.036, N = 189, TCGA LUAD miRNAseq data). By subsequent CMAp analysis we then identified drugs that significantly affect expression of the COPD-associated genes in a manner that may improve the patients prognosis, and those that may cause side effects. First mentioned include fenpiride – drug for obstructive airways disease and urological anti-infective phenazopyridine. Interestingly, we found calcium folinate - frequently used as a detoxifying agent for antineoplastic treatment, including treatment of lung cancer, as a potentially harmful. Conclusion: Genes and microRNAs associated with COPD are significantly associated with prognosis of the lung cancer patients.

Keywords: pharmacogenomics, Non-small-cell lung cancer, Chronic obstructive pulmonary disease

POSTER SESSION 3 - P3.01: BIOLOGY/PATHOLOGY
MODELS OF LUNG CANCER – WEDNESDAY, DECEMBER 7, 2016

P3.01-053 MOUSE MODELS OF PRIMARY LUNG CANCER - A THOROUGH EVALUATION
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Background: Lung cancer is the most prominent cancer in human with the highest mortality rate among cancer patients in both genders nowadays. Several models of primary lung cancer research are in use, however, no systematic evaluation of optimal models is available. Here, we assess and reappraise the most robust models of primary lung cancer for their suitability of cancer evolution and targetability for new therapeutics. Methods: Three models of primary lung cancer were evaluated: (I) Carcinogen (urethane or nitrosodimethylamine (DEN)) induced lung cancer model, established via three intraperitoneal (i.p.) injections to BALB/c and C57BL/6 mouse strains. Five and ten months after injections, mice were assessed for tumor incidence. Lewis Lung Carcinoma (LLC) cell line was employed for an orthotopic development of lung tumor in syngeneic mouse. The cell line was injected (i) intravenously (i.v.) or (ii) subcutaneously (s.c.) to establish lung tumor models in 14 days. Tumor nodules and tumor necrosis were confirmed by microscopy. Immunohistochemistry (IHC) of markers of proliferation (p-Histone3, inhibitor of differentiation 1 (id1), and Ki67), immune cells (CD4, CD8, B220, F4/80, and NKP46), vascular structure (CD31), stroma (alpha-actin) were performed for a finer characterization of the tumor. Results: Ten months after i.p. injections of carcinogens, we found that the urethane model stably induced tumor nodules (90%: 9/10) when compared to DEN (30%: 3/10). BALB/c strain was significantly more susceptible for the urethane induced tumor development compared to C57BL/6. Injection of LLC cells i.v. developed diffuse lung tumor without metastasis to other organs. s.c. injection also stably developed single tumor nodule (~500mg). IHC revealed that all tumors were consistently positive for the proliferation markers, and CD4/80+ cells and CD4+ cells infiltrated into tumors significantly more than CD8+ B220+, or NKP46+ cells. Heterogeneous distributions of CD31+ cells and alpha-actin+ cells were observed in overall tumor models. Conclusion: The urethane-induced lung tumor is reliable and reproducible with a high rate of development and seems superior to DEN induced tumor, but need a long time period to develop. In contrast, the i.v. and s.c. tumor models are established within short time ranges. The tumors developed by s.c. enable for the analysis of the tumor only without adjacent tissue bias. The involvement and characteristics of immune cells found within tumors were comparable across all models. Injections by i.v. or s.c. of cell line to mouse can be considered as an alternative yet convenient model to develop various different types of lung cancers.

Keywords: Lung; Cancer; Animal model

References
Background: We have identified a novel serine/threonine protein kinase, MAP3K19, whose expression in normal lung was predominantly localized to alveolar and interstitial macrophages, bronchial epithelial cells and type II pneumocytes of the epithelium. We have also found MAP3K19 to be expressed in multiple, primary NSCLC tumor samples, as well as human lung cancer cell lines, including A549. The kinase is transcriptionally upregulated in cells upon various types of cell stress, including oxidative, endoplasmic reticulum and osmotic stress. Methods: Using two different murine xenograft models, we assayed the role of MAP3K19 to inhibit the growth of either primary human NSCLC tumors and A549 cells using small molecule inhibitors. Results: The ability of i.v. injected A549 cells to colonize and grow in the lung was significantly reduced in mice that received orally administered, selective MAP3K19 inhibitors. Similar results were observed in a subcutaneous xenograft model, as A549 tumor cell growth was inhibited by both MAP3K19 antagonists and other standard of care kinase inhibitors. These studies also showed an additive anti-proliferative effect when gefitinib or sorafenib and MAP3K19 inhibitors were co-administered. Importantly, xenograft models using primary human NSCLC tumors implanted subcutaneously in immunodeficient mice showed a statistically significant inhibition of tumor growth when the mice were treated with the orally administered MAP3K19 antagonists. IHC analysis of the tumors showed that mice treated with the MAP3K19 inhibitors also had decreased levels of Ki-67, c-myc, p27 and phospho-Bim staining and increased caspase-3 staining. Conclusion: These results suggest a molecular mechanism by which MAP3K19 may inhibit tumor cell growth, and further suggest that inhibition of MAP3K19 either by itself or in combination with other therapies may represent a new avenue for the treatment of NSCLC. The clinical development of the MAP3K19 inhibitor is expected to initiate Phase I clinical trials in early 2017.

Keywords: NSCLC, MAP3K19, novel kinase

POSTER SESSION 3 – P3.01: BIOLOGY/PATHOLOGY
Stem Cells in Lung Cancer – WEDNESDAY, DECEMBER 7, 2016

P3.01-055 IN VITRO CONSTRUCTION OF LUNG CANCER STEM LIKE CELLS
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Background: Lung cancer stem cells are considered to be responsible for lung cancer progression. However, little is known about how they actually promote lung cancer progression and metastasis. Methods: We retrovirally introduced three defined factors (OCT3/4, SOX2, and KLF4) into lung cancer cell line, A549. We evaluated cancer stem cell properties in the A549 cells transduced with the three factors (OSK-A549) in terms of their chemo resistance, and sphere formation ability. We also assessed lung cancer organoid constructing ability by co-culturing with mesenchymal stem cells (MSC) and human umbilical vein epithelial cells (HUVEC). Results: OSK-A549 cells formed dome-shaped colonies in 10 to 15 days after transfection. These colonies were picked up for further expansion in DMEM/10%FBS medium, and we named these cells OSK-A549-Colony cells. Induced OSK-A549-colony cells were more resistant to cisplatin than parental A549 cells. Cell cycle analysis revealed that the rate of Go/G1 cells was significantly increased in OSK-A549-colony cells. Sphere forming ability was enhanced in OSK-A549-colony cells. These results suggested that OSK-A549-colony cells acquired the properties of lung cancer stem like cells. Co-culture with MSC and HUVEC showed that A549 and OSK-A549-colony cells could form much denser spheres than those of parental cells (Figure). As the morphology was similar to real lung cancer tissue, we named this spheres “lung cancer organoids”.

Conclusion: By introducing defined factors, A549 cells acquired lung cancer stem cell like properties, and these cells could form lung cancer organoids by co-culturing with MSC and HUVEC. Analysis of these organoids might enable us to elucidate the molecular mechanism of lung cancer progression and metastasis.

Keywords: cancer organoid, lung cancer, Cancer stem cell

POSTER SESSION 3 – P3.01: BIOLOGY/PATHOLOGY
STEM CELLS IN LUNG CANCER – WEDNESDAY, DECEMBER 7, 2016

P3.01-056 ASSOCIATION OF ANGIogenesis, EMT AND STEM CEll CHARACTERISTICS USING HYPOXIC STRESS IN LUNG CANCER
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Background: Hypoxia, a major phenomenon in solid tumors, can promote the metastatic potential of tumor cells which is associated with chemoresistance and poor prognosis. It was reported that various angiogenesis factors including VEGF and HIF, were associated in cancer development and progression by hypoxia. In addition, both epithelial-mesenchymal transition (EMT) and cancer stem cells play an important role in malignant progression in many human tumors. We investigated the effect of hypoxic stress on the angiogenesis, EMT and stemness acquisition in lung cancer. Methods: Normal lung cell (BEAS-2B) and lung cancer cell lines (A549, H222, H226 and H460) were incubated in either normoxic or hypoxic (below 1% O2) conditions. For transcriptome analysis, mRNA of BEAS-2B and A549 cells line were analyzed using next-generation sequencing (HiSeq 2500 system). For further validation, angiogenesis markers were analyzed by western blotting. EMT was assessed with western blotting, wound healing assay and Matrigel invasion assay, and stem cell characteristics were assessed with RT-PCR, immunostaining, soft agar colony formation assay, sphere formation assay and in vivo mice tumor model. Results: Next-generation sequencing revealed significant changes in the expression of angiogenesis, EMT and stem cell markers after hypoxic stress. Among the angiogenesis markers, VEGF and HIF-1α were increased. EMT markers related in hypoxia showed decrease in E-cadherin and increase in fibronecin, vimentin, N-cadherin, α-SMA, Snail, Slug, ZEB1 and ZEB2. Stem cell markers such as CXCR4, Oct4 and Nanog were increased at least one lung cancer cell line in hypoxic condition compared with in normoxic condition. Functional assays for EMT and stemness acquisition indicated that hypoxic stress increased wound healing, Matrigel invasion, sphere formation and in vivo mice tumor formation. Conclusion: These results suggest that hypoxia induces angiogenesis markers expression which is associated with EMT and stemness acquisition in lung cancer. Keywords: hypoxic stress, angiogenesis, lung cancer

POSTER SESSION 3 – P3.01: BIOLOGY/PATHOLOGY
STEM CELLS IN LUNG CANCER – WEDNESDAY, DECEMBER 7, 2016

P3.01-057 TGF-B: INDUCED EMT AND STEMNESS CHARACTERISTICS IN LUNG CANCER
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Abstracts

Background: Transforming growth factor-β (TGF-β) is known to inhibit cell growth in benign cells but promotes tumor invasion and metastasis by inducing an epithelial-mesenchymal transition (EMT). EMT is a differentiation switch through which epithelial cells differentiate into mesenchymal cells. It occurs in the process of tissue morphogenesis during development, wound repair and cancer progression in adult tissues. EMT is often associated with acquisition of stem-like characteristics. In this study, we investigated whether EMT induced by TGF-β could acquire stem-like characteristics in lung cancer. Methods: Human normal epithelial (BEAS-2B) and cancer (A549, H2292, H266 and H460) cell lines were incubated with 10 ng/ml of TGF-β for 3 days. Transcriptome and methylation analysis of BEAS-2B and A549 cells treated with TGF-β were performed by using next-generation sequencing (HiSeq 2500 system). Western blotting was performed to analyze the expression of epithelial marker (E-cadherin) and mesenchymal markers (fibronectin, vimentin, N-cadherin and α-SMA). RT-PCR was performed to analyze the expression of variable stem cell markers (CD44, CD133, CXCXR4, ABCG2, CD117, ALDH1A1, EpCAM, CD90, Oct4, Nanog, SOX2, SSEA4, and CD166). Wound healing assay, Matrigel invasion assay and sphere formation assay were used to assess functional characteristics of EMT and stemness acquisition. Results: Next-generation sequencing revealed significant changes in the expression of stem cell markers, CD44, ALDH1A1 and CD100 in both BEAS-2B and A549 cells. The changes in the expression of EMT and stem cell markers induced by TGF-β were variable according to lung cell lines. Except for H460 cell line, lung cell lines showed at least one or more increased stem cell marker expression with TGF-β. Functional analysis revealed increased wound healing, Matrigel invasion and sphere formation after TGF-β treatment. Conclusion: TGF-β induced EMT was associated with acquisition of stem-like characteristics. Various expression patterns of stem cell markers were observed according to different lung cancer cell lines.

Keywords: lung cancer, TGF-β, epithelial-mesenchymal transition, stemness

P3.01-058 DEMETHYLATION OF CXCR4 AND STEMNESS ACQUISITION IN LUNG CANCER

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Background: As a cancer stem cell marker, CXCR4 has been known to be closely associated with cell survival and stemness acquisition. Previous studies reported that the level of CXCR4 is increased after hypoxic condition in several types of cancer. However, the mechanism of the increased CXCR4 expression has not been well understood. We investigated whether aberrant promoter demethylation could induce CXCR4 activation by hypoxic stress in lung cancer. Methods: Human normal lung cell (BEAS-2B) and lung cancer cell lines (A549, H2292, H266 and H460) were incubated under hypoxic condition. Transcriptome and methylation analysis using next-generation sequencing were performed by HiSeq 2500 system. For further validation, CXCR4 expression was analyzed by RT-PCR and western blotting. To determine whether CXCR4 is reactivated, cell lines were treated with a DNA methyltransferase inhibitor (AZA). Hypoxia-induced DNA demethylation was identified by methylation-specific PCR and bisulfite sequencing. Stem cell characteristics were assessed by sphere formation assay and in vivo mice tumor model. Results: Next-generation sequencing results revealed that CXCR4 expression was increased after hypoxic condition, whereas CXCR4 methylation was reduced. CXCR4 was activated by either hypoxic condition and treatment with AZA. MSP showed decreased CXCR4 promoter methylation in hypoxic condition compared with normoxic condition. Functional stem cell assay indicated that hypoxic stress increased sphere formation and in vivo mice tumor formation. Conclusion: These results suggest that hypoxia induces stem cell characteristics which are related with CXCR4 reactivation by promoter demethylation.

Keywords: demethylation, CXCR4, stemness, lung cancer

P3.01-060 APTAMERS AS A TOOL TO DETECT LUNG CANCER STEM CELLS

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Background: Cancer stem cells (CSC) are a subpopulation of cells in the tumor with capacity for self-renewal and differentiation. Due to these characteristics, CSC are referred to as tumor initiating cells. Several studies suggest that CSC might be responsible for metastasis and resistance to conventional therapies leading to tumor recurrence. A challenge in cancer biology is to discover the biomarkers for specific types of cancer and the development of probes capable of identifying these targets. Thus, the objective of this study is the development of DNA aptamers for selective identification of the molecular signature of lung CSC. Methods: A549 lung carcinoma cells were used as target to perform the isolation of aptamers from a random library of DNA through the cell SELEX technique. For negative cycles for removal of DNA molecules binding to common epitopes between different cell types, blood cells were used. Results: CSC from A549 were expanded in vitro as tumorspheres and stemness marker expression profiles analyzed by

P3.01-059 A STEM-CELL ORIENTED PHYLOGENY OF NON-SMALL CELL LUNG CANCERS

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Background: The degree of histologic cellular differentiation of a lung cancer has been associated with prognosis but is subjectively assessed. We hypothesized that information about tumor differentiation of individual cancers could be derived objectively from cancer gene expression data, and would allow creation of a cancer phylogenetic framework that would correlate with clinical, histologic and molecular characteristics of the cancers, as well as predict prognosis. Methods: We utilized mRNA expression data from NSCLC samples to explore the utility of ordering samples by their distance in gene expression from that of stem cells. A differentiation baseline was obtained by including expression data of human embryonic stem cells (hESC) and human mesenchymal stem cells (hMSC) for solid tumors, and of hESC and CD34+ cells for liquid tumors. Results: We found that the correlation distance (the degree of similarity) between the gene expression profile of a tumor sample and that of stem cells oriented lung cancers in a clinically coherent fashion. Cancers most similar to stem cells in gene expression are in general undifferentiated, larger, more likely to be node positive and more FDG avid on PET imaging. Most importantly, patients with cancers with gene expression patterns most similar to that of stem cells had poorer overall survival.

Conclusion: A stem cell oriented phylogeny of lung cancers objectively orients cancers by level of differentiation in a clinically coherent fashion. Lung cancers most similar to stem cells in expression are associated with a poorer prognosis after treatment.

P3.01-059 A STEM-CELL ORIENTED PHYLOGENY OF NON-SMALL CELL LUNG CANCERS

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Background: The degree of histologic cellular differentiation of a lung cancer has been associated with prognosis but is subjectively assessed. We hypothesized that information about tumor differentiation of individual cancers could be derived objectively from cancer gene expression data, and would allow creation of a cancer phylogenetic framework that would correlate with clinical, histologic and molecular characteristics of the cancers, as well as predict prognosis. Methods: We utilized mRNA expression data from NSCLC samples to explore the utility of ordering samples by their distance in gene expression from that of stem cells. A differentiation baseline was obtained by including expression data of human embryonic stem cells (hESC) and human mesenchymal stem cells (hMSC) for solid tumors, and of hESC and CD34+ cells for liquid tumors. Results: We found that the correlation distance (the degree of similarity) between the gene expression profile of a tumor sample and that of stem cells oriented lung cancers in a clinically coherent fashion. Cancers most similar to stem cells in gene expression are in general undifferentiated, larger, more likely to be node positive and more FDG avid on PET imaging. Most importantly, patients with cancers with gene expression patterns most similar to that of stem cells had poorer overall survival.

Conclusion: A stem cell oriented phylogeny of lung cancers objectively orients cancers by level of differentiation in a clinically coherent fashion. Lung cancers most similar to stem cells in expression are associated with a poorer prognosis after treatment.

P3.01-060 APTAMERS AS A TOOL TO DETECT LUNG CANCER STEM CELLS

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Background: Cancer stem cells (CSC) are a subpopulation of cells in the tumor with capacity for self-renewal and differentiation. Due to these characteristics, CSC are referred to as tumor initiating cells. Several studies suggest that CSC might be responsible for metastasis and resistance to conventional therapies leading to tumor recurrence. A challenge in cancer biology is to discover the biomarkers for specific types of cancer and the development of probes capable of identifying these targets. Thus, the objective of this study is the development of DNA aptamers for selective identification of the molecular signature of lung CSC. Methods: A549 lung carcinoma cells were used as target to perform the isolation of aptamers from a random library of DNA through the cell SELEX technique. For negative cycles for removal of DNA molecules binding to common epitopes between different cell types, blood cells were used. Results: CSC from A549 were expanded in vitro as tumorspheres and stemness marker expression profiles analyzed by
flow cytometry. Flow cytometry comparing the cells labeled with the initial library or with the selected aptamers, showed in the latter a large increase in the labeled population. This highly fluorescence-tagged aptamer-labeled cell population was also positive for CD90, described as a marker for cancer stem cells. This double-labeled population was isolated by cell sorting with the aptamers being purified from the cells, sequenced and grouped into families based on homology between sequences. Eight aptamers were identified, whose affinity and specificity are currently being analyzed. Conclusion: The selected aptamers are able to identify a subpopulation of cells, which express stem cell markers. Financial support: FAPESP; CNPq (Brazil)

Keywords: Cancer Stem Cells, Phenotypic markers, Aptamers, Molecular Signature of Membrane

P3.01-061 PROGNOSTIC SIGNIFICANCE OF STEM-CELL-RELATED MARKER EXPRESSION AND ITS CORRELATION WITH HISTOLOGIC SUBTYPES IN LUNG ADENOCARCINOMA

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Background: Cancer stem cells (CSCs) are a small subset of tumor cells that exhibit stem cell-like properties and contribute in treatment failure. CSCs can be distinguished from other cancer cells on the basis of specific markers. Although the clinical impact of these markers is unclear, they may have a prognostic or predictive value in NSCLC. Methods: To clarify the expression and prognostic significance of several CSC markers in non-small cell lung cancer, we retrospectively analyzed 368 patients with adenocarcinoma (n = 226) or squamous cell carcinoma (n = 142). We correlated the expression of six CSC markers – CD133, CD44, aldehyde dehydrogenase 1 (ALDH1), sex determining region Y-box 2 (SOX2), octamer binding transcription factor 4 (OCT4), and Nanog – with clinicopathologic and molecular variables and survival outcomes. Results: In adenocarcinoma, CD133, ALDH1 and CD44 expression was associated with low pathologic stage and absence of lymphovascular invasion, while Nanog expression correlated with high histologic grade, lymphatic invasion and increased expression of Snail-1, a transcription factor associated with epithelial-mesenchymal transition. CSC marker expression was also associated with histologic subtypes in adenocarcinoma. Multivariate analysis showed that high Nanog expression was an independent factor associated with a poor prognosis in adenocarcinoma. Conclusion: In conclusion, we have shown that CSC markers may be prognostic factors in NSCLC, and high Nanog expression is an independent prognostic factor for poor survival that may be associated with EMT features in ADC patients. In addition, the clinicopathologic implication of CSC markers in lung ADC differed from those in tumors arising from other organs. Thus, the impact of CSC marker expression should be considered in a tumor/organ specific manner.

Keywords: Cancer stem cell marker, lung adenocarcinoma, NANOG, non-small cell lung cancer

P3.01-062 PROFILING DNA METHYLATION AND GENE EXPRESSION ON CANCER STEMNESS REPROGRAMMING IN LUNG ADENOCARCINOMA

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Background: The cancer stemness niche that could promote and induce the reprogramming of cancer stem cells (CSCs), is considered as one of the key factors in cancer metastasis, tumor recurrence and drug resistance. The behaviour of this specific tumor microenvironment may correlate with poor prognosis of the disease. However, the contribution of the cancer stemness niche on regulating the differentiation or de-differentiation of CSCs remains unclear. Methods: To investigate the mystery of the niche and to discover the genetic and epigenetic machineries along the reprogramming process; here, us cells in a 3D co-culture model, integrating with both genome-wide transcriptome and DNA methylation, the gene expression and DNA methylation patterns were analyzed in lung CSCs and the differentiated clones. Results: We found that the stromal cells- incubated lung CSCs (StriCLS1) were significantly characterized as the CSC enriched population; with highly expressed stemness makers, nanog, oct3/4, sox2, and klf4, and showed relatively higher percentages of side population, ALDH activity and tumorigenicity than differentiated cells in both in vitro tumor sphere forming ability and in vivo xenograft model (only 10 StriCLS1 cells could generate tumor formation in NGS mice). We found that these stemness characteristics diminished as removing the feeder stroma cells and could be restored after re-co-culture with the tumorous stroma cells. Although the whole exon-seq data showed the comparability of StriCLS1 and differentiated CLS1 CSCs on the DNA sequences; the gene expression and DNA methylation patterns revealed significantly changes. The results showed that stemness and its reprogramming were related to paracrine/autocrine networks (IGFBPs, WNTs/Hedgehog, HGF/Met, LIF/LIFR), metabolism shift (PDGs and LDHs), and other drug-resistance or stress-response signalings (ABC2G and AKTs), indicating that these key factors were regulated via the niche which may be affected by the DNA methylation patterning. Conclusion: We conclude that the cancer stemness reprogramming is a well regulatory process via the paracrine/autocrine connective networks in the tumor microenvironment. This process may contribute to cancer progression, and assist the tumor growth and evolution under different stresses. This study provides new insights into the importance of crosstalk between CSCs and the cancerous microenvironment that could be targeted as potential genetic/epigenetic signaling regulators for anticancer therapy.

Keywords: Cancer Stem Cells, Transcriptomics/Epigenomics, microenvironment, Cancer Stemness Niche

P3.01-063 XIAP INHIBITS MATURE SMAC INDUCED APOPTOSIS BY DEGRADING IT THROUGH UBIQUITINATION IN NSCLC

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Background: XI-linked inhibitor of apoptosis protein (XIAP) and second mitochondrial-derived activator of caspase (Smac) are two important prognostic biomarkers for cancer. They are negatively correlated in many types of cancers. However, their relationship is still unknown in lung cancer. Methods: RT-PCR and Western blot were performed to explore the correlation between Smac and XIAP at the mRNA and protein level. Results: Full-length XIAP, Smac and mature Smac were generated by PCR and cloned into pcDNA3.0-Flag/Myc. The location of mature Smac and full-length Smac was detected by immunofluorescence. MTT assay and Flow cytometry were detected the cell viability and apoptosis of transfected cells. Caspase-3 activity was measured by Caspase-3 activity assay. Co-immunoprecipitation assay was done to reveal the direct relationship between XIAP and Smac. Nude mouse xenograft experiment further proved the relation and the function of Smac and XIAP in vivo. Results: In this study, we found that there was a negative correlation between Smac and XIAP at the level of protein but not mRNA in NSCLC patients. However, XIAP overexpression had no effect on degrading endogenous Smac in lung cancer cell lines. Therefore, we constructed plasmids with full length of Smac (fSmac) and mature Smac (mSmac) which located in cytoplasm instead of original mitochondrial location, and confirmed by immunofluorescence. Subsequently, we found that fSmac rather than mSmac was degraded by XIAP and inhibited cell viability. CHX chase assay and ubiquitin assay were performed to illustrate XIAP degraded mSmac through ubiquitin pathway. Overexpression of XIAP partially reverted apoptotic induction and cell viability inhibition by mSmac, which was due to inhibiting caspases-3 activation. In nude mouse xenograft experiments, mSmac inhibited K67 expression and slowed down lung cancer growth, while XIAP partially reversed the effect of mSmac by degrading it. Conclusion: In conclusion, XIAP inhibits mature Smac-induced apoptosis by degrading it through ubiquitination in NSCLC.

Keywords: apoptosis, XIAP, NSCLC, Smac

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P3.01-064 THE OVEREXPRESSION AND CLEAVAGE OF SASHI BY CASPASE-3 STIMULATES CELL DEATH IN LUNG CANCER CELLS
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Background: SASH1 (SAM and SH3 domain-containing protein 1) is a recently identified gene with tumour suppressor properties and has a role in induction of apoptosis. Previous work has shown that 90% of lung cancer cell lines have a decrease in SASH1 mRNA levels (Zeller et al, 2003), however little characterisation of SASH1 function in lung cancer has been undertaken. Methods: We evaluated SASH1 expression in transformed normal and malignant non-small cell lung cancer cell lines. We also utilised cell based assays to study the effects of altered SASH1 levels on cell survival and proliferation. Identification of a novel SASH1 targeting drug was performed through connectivity mapping. Results: SASH1 protein expression was down regulated in two of the five lung cancer cell lines compared to immortalized normal bronchial epithelial cells. Prognosis assessment identified decreased SASH1 mRNA expression reduced patient survival. The depletion of SASH1 in lung cells resulted in a significant increase in cellular proliferation in cancer lung cells. Connectivity mapping predicted the drug Chloropyramine would lead to an increase in SASH1 expression. We demonstrated that Chloropyramine upregulates SASH1 in malignant cell lines. In keeping with this we have demonstrated the Chloropyramine inhibited lung cancer proliferation in vitro. We also explored the role of SASH1 in apoptosis. Following ultraviolet light exposure SASH1 is cleaved by Caspase-3. The C-terminal fragment of SASH1 then translocates from the cytoplasm to the nucleus where it associates with chromatin. The overexpression of wild type SASH1 or cleaved SASH1 amino acids 231-1247 leads to an increase in apoptosis, however loss of the SASH1 cleavage site and/or nuclear translocation prevents this initiation of apoptosis. Mechanistically SASH1 cleavage is required for the translocation of the transcription factor NF-κB to the nucleus. The use of the NF-κB inhibitor DHMEQ demonstrated that the effect of SASH1 on apoptosis was dependent on NF-κB, indicating a co-dependence between SASH1 and NF-κB for this process. Conclusion: We have shown that SASH1 contributes to apoptosis via a NF-κB-dependent mechanism. Agents that upregulate SASH1, such as chloropyramine or SASH1 gene therapy, are potential novel approaches to the management of NSCLC in the future.
Keywords: SASH1, Chloropyramine, lung cancer, apoptosis

POSTER SESSION 3 – P3.02a: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/IMMUNOTHERAPY
ALK – WEDNESDAY, DECEMBER 7, 2016
P3.02-a-001 Response and plasma genotyping from phase I/II trial of enartibin (X-396) in patients (pts) with ALK+ NSCLC
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Background: Enartibin (X-396) is a novel, potent anaplastic lymphoma kinase (ALK) small molecule tyrosine kinase inhibitor (TKI) with additional activity against MET, ABL, Axl, EphA2, LTK, and ROS1 and SLK. We report data on the ALK TKI-naive and crizotinib (C)-resistant NSCLC pts treated with enartibin. Clinical trial methods: NCT01625234 Methods: In this multicenter expansion study, pts with ALK+ NSCLC were treated with enartibin 225 mg daily on a 28-day schedule. Pts had measurable disease, ECOG PS 0-1, and adequate organ function. Untreated brain metastases (CNS) and leukemogenous disease were excluded. Next Generation Sequencing (NGS) was performed on plasma samples collected at baseline and on study and compared with central tissue results (FISH/HC). All pts were assessed for response to therapy using RECIST 1.1 and for adverse events (AEs) using CTCAE version 4.03. Results: 80 pts (51% female) have been enrolled. Median age 54 (19-81 years), 64% ECOG PS 1. Pts had a history of ALK + NSCLC (51/80 pts). CNS responses were observed in 42/80 pts; partial response (PR) was achieved in 23 pts (28%) and stable disease (SD) in 8 pts (20%). In the C-naive pts (n = 8), PRs were observed in 7 pts (88%). In the 22 pts with prior C but no other ALK TKI, 14 pts (64%) achieved PR and 6 (27%) SD. In the 10 pts who had received two or more prior ALK TKIs, there was 2 PR, 2 SD (40% DCR). CNS responses (50% PR) have been observed in both C-naive and C-Resistant pts. Plasma and tissue genotyping were available on 27 pts (26 ALK+ and 1 ALK). ALK was detected in plasma in 16 pts, all of whom had a response to therapy. 2 pts with PD were tissue +ve and plasma -ve. 9 plasma samples were un evaluable. Serial sequencing demonstrated a decrease in ALK in pts responding and an increase at the time of progression. The most common drug-related AEs (≥20% of pts) included rash (53%), nausea (32%), vomiting (26%), fatigue (23%), and pruritus (21%). Most AEs were Grade (G) 1-2. The G3 treatment-related AEs were rash (8 pts), fatigue (2 pts), pruritus (2 pts), edema (2 pts), decreased appetite (1 pt), nausea (1pt), and vomiting (1pt). Conclusion: Enartibin is well-tolerated with response in both C-naive and C-Resistant ALK+ NSCLC pts, as well as pts with CNS disease. Plasma sequencing appears to be promising to select pts for therapy and monitor for response and development of acquired resistance.
Keywords: Nextgen Sequencing, ALK, NSCLC

P3.02a-002 Pulmonary Sarcomatoid Carcinoma with ALK Rearrangement: Frequency, Clinical-Pathologic Characteristics, and Response to ALK Inhibitor
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Background: Pulmonary sarcomatoid carcinoma (PSC) is a poorly differentiated subtype of non-small cell lung cancer (NSCLC). Compared with other subtypes of NSCLC, PSC has higher aggressive courses and far worse survival. The incidence of anaplastic lymphoma kinase (ALK) rearrangement is controversial, and clinical benefit from anti-ALK treatment in PSC remains unknown. This study aimed to reveal the reliable frequency and the clinical-pathologic characteristics of pulmonary sarcomatoid carcinoma (PSC) with anaplastic lymphoma kinase (ALK) rearrangement, and to provide insight into the translatability of anti-ALK treatment in this treatment-refractory disease. Methods: Immunohistochemistry (IHC) staining using a monoclonal anti-ALK (DSF3) rabbit monoclonal antibody was performed in 141 PSC specimens collected from multiple medical centers. IHC-positive cases were then confirmed using ALK fluorescent in situ hybridization (FISH). The incidence rates of ALK rearrangement-positive by IHC and then were confirmed by FISH. The relationship of ALK rearranged PSC were then analyzed. Response to the ALK inhibitor crizotinib in a patient with ALK rearranged PSC was evaluated according to the response evaluation criteria for solid tumors (RECIST) version 1.1. Results: A total of 5/141 (3.5%) of PSC showed ALK rearrangement-positive by IHC and then were confirmed by FISH. There were carcinomasarcoma, and the other three were pulmonary pleomorphic carcinoma (PPC). Strong positive ALK rearrangement was observed in both the epithelial and sarcomatoid components. ALK rearrangement was mutually exclusive with mutations in EGFR and KRAS. The median age of ALK-positive patients was younger than that of ALK-negative patients. PSCs in never-smokers was more likely to harbor ALK rearrangement than those in former or current smokers (P <0.05). A 60-year-old woman diagnosed with ALK-rearranged PSC experienced a partial response (32%) to the ALK inhibitor crizotinib. Conclusion: The incidence rates of ALK rearrangement in PSC in the Chinese population are similar to those of other subtypes of NSCLC. PSCs in younger never-smokers are more often to harbor ALK rearrangement.
ALK inhibitors may serve as an effective treatment for ALK-rearranged PSC.

Keywords: Pulmonary sarcomatoid carcinoma, anaplastic lymphoma kinase rearrangement, clinical-pathologic characteristics, frequency
Abstracts

Keywords: fluorescence in situ hybridization, ALK Inhibitor, immunohistochemical staining, Anaplastic lymphoma kinase

POSTER SESSION 3 – P3.02A ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/IMMUNOTHERAPY
ALK BIOMARKERS – WEDNESDAY, DECEMBER 7, 2016

P3.02A-006 IMMUNE RECOGNITION OF ALK FUSION PROTEINS IN PATIENTS WITH ALK-REARRANGED NON-SMALL CELL LUNG CANCER
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Background: Although several tyrosine kinase inhibitors have potent antitumor activity against ALK-rearranged non-small cell lung cancers (NSCLC), resistance emerges through a number of mechanisms. Preclinical evidence suggests that ALK-positive NSCLCs can also be successfully targeted immunologically using vaccine-based approaches. Immunologic responses against the ALK protein have been reported in ALK-positive anaplastic large cell lymphoma, and we sought to determine whether ALK could be recognized by the immune systems of patients with ALK-positive NSCLC. Methods: Serum was collected from 32 ALK-positive and 29 ALK-negative NSCLC patients over the course of routine clinical care who had consented to an institutional review board approved translational research protocol. We developed a novel enzyme-linked immunosorbent assay (ELISA) to detect anti-ALK antibodies against the ALK cytoplasmic domain in patients with ALK rearranged NSCLC, and the specificity of these autoantibodies was validated using Western blot analysis. Short peptides spanning the length of the ALK cytoplasmic domain were synthesized to more narrowly define the precise immunogenic peptide sequences. Results: Among 32 ALK-positive NSCLC patients, very high ALK autoantibody titers were detected in the serum of 3 patients (9%), and ALK autoantibodies were not detected in any of the 29 patients with ALK-negative NSCLC. These autoantibodies specifically recognized only the ALK cytoplasmic domain and not the ALK extracellular domain. Epitope mapping demonstrated that the autoantibodies from each of the 3 patients with high autoantibody titers recognized distinct ALK peptide sequences within the ALK cytoplasmic domain. Conclusion: ALK is capable of being recognized by the immune systems in some patients with ALK-positive NSCLC. Further investigation is needed to determine whether the presence of anti-ALK antibodies impacts prognosis in NSCLC. The naturally immunogenic properties of ALK in NSCLC may be able to be exploited using therapeutic ALK vaccines in patients.

Keywords: ALK, Immunology, autoantibodies

POSTER SESSION 3 – P3.02A ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/IMMUNOTHERAPY
ALK BIOMARKERS – WEDNESDAY, DECEMBER 7, 2016

P3.02A-007 MONITORING FOR AND CHARACTERISTICS OF CRIZOTINIB PROGRESSION: A CHART REVIEW OF ALK+ NON-SMALL CELL LUNG CANCER PATIENTS
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Background: Crizotinib is recommended as first-line therapy for non-small cell lung cancer (NSCLC) patients with ALK rearrangements. Following the approval of second-generation ALK inhibitors for patients who progress on or are intolerant to crizotinib, this study describes how physicians monitor for progression, diagnose progression, and alter treatments following progression on crizotinib therapy. Methods: A panel of US oncologists was surveyed regarding their monitoring practices and criteria for diagnosing progression on crizotinib. From March to June 2016, the oncologists provided data retrospectively from the medical charts of their adult patients diagnosed with locally-advanced or metastatic ALK+ NSCLC who progressed on crizotinib following the US approval of the first second-generation ALK inhibitor, ceritinib, in April 2014. Time to clinician-defined progression and treatment changes following progression were assessed using the medical chart data.

Results: 28 oncologists responded to the survey. Data was abstracted on 74 ALK+ NSCLC patients who progressed on crizotinib. 49% of the patients were male; 50% were never smokers. 81% of patients received crizotinib in first line, the median age at initiation was 61 years. Most physicians (77%) reported monitoring for radiographic progression every 3-4 months. In terms of course of action when new lesions are detected, physician response varied: most physicians (75%) prefer to add local therapy and resume crizotinib following a symptomatic isolated lesion, while, following multiple symptomatic lesions, 96% and 66% of physicians prefer to switch to a new therapy depending upon whether the lesions were systemic or isolated to the brain, respectively. Among the study sample, progression on crizotinib, as defined by physicians, was detected after a median of 10.4 months. 86% of patients discontinued crizotinib within 30 days of diagnosis of the physician-defined progression. Among all patients who discontinued, 77% switched to ceritinib, 14% to chemotherapy, and 1% to alectinib; the remaining 7% did not receive additional systemic antineoplastic therapy. Conclusion: The findings from this physician survey and retrospective chart review of ALK+- NSCLC crizotinib-treated patients suggest that physician response to the development of new lesions varies depending upon the location and extent of the lesions. Once physicians considered their patients to have progressed, most immediately switched their patients to ceritinib, a second-generation ALK inhibitor.

Keywords: progression, Monitoring, non-small cell lung cancer, Anaplastic lymphoma kinase

POSTER SESSION 3 – P3.02A ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/IMMUNOTHERAPY
ALK BIOMARKERS – WEDNESDAY, DECEMBER 7, 2016

P3.02A-008 EML4-ALK IN PLASMA EXOSOMES FROM A COHORT OF NSCLC PATIENTS
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Background: The identification of EML4-ALK translocations in 3%-5% of NSCLC resulted in the approval of numerous targeted therapies of these lung cancers. Consequently, the availability of new ALK inhibitors forced the development of diagnostic assays, although their validation is limited by the restricted number of available specimens. As the significance of the current standard test (tissue-based FISH) is progressively questioned, development of improved accompanying diagnostics for the predictive biomarker is of high medical need. Overcoming discrepancies of FISH such as tissue sample availability and inter-observer variability, we validated a liquid biopsy test for analysis of EML4-ALK fusion transcripts. For the first time, the availability of a defined cohort of NSCLC patients allowed the determination and clinical interpretation of EML4-ALK in exosomal RNA derived from plasma specimen. Methods: We developed and validated an exosome-based biopsy test for EML4-ALK to be run in a CLIA laboratory. The assay enables the discriminative detection of the three major fusion variants v1, v2 and v3(a,b,c), in detail, exosomal RNA is isolated from low-volume plasma (≤2ml) of NSCLC patients and subjected to highly sensitive and specific RT-qPCR. During analysis, each sample is confirmed by definition of controls and designed for a valid result. The final diagnostic results of all clinical specimen are correlated with clinical response data. Results: Section is not applicable. Cohort analysis is ongoing. Therefore, we will submit our results as late-breaking abstract. Conclusion: Section not applicable. We will determine the variant-specific expression of EML4-ALK in plasma samples of a clinically defined, medium-sized NSCLC cohort. Based on specimen data, we are able to test for correlation of the biomarker derived from exosomes with respective tissue results and clinical response of a patient.

Complete results and conclusions will be based on the analysis of all clinical samples. As the respective cohort is currently in the status of sample collection and testing for EML4-ALK (ongoing until October 2016), the final data will be submitted as late-breaking abstract.

Keywords: EML4-ALK, liquid biopsy, exosomes, Diagnostics

POSTER SESSION 3 – P3.02A ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/IMMUNOTHERAPY
ALK BIOMARKERS – WEDNESDAY, DECEMBER 7, 2016

P3.02A-009 TPX-0005: A MULTI-FACETED APPROACH TO OVERCOMING CLINICAL RESISTANCES FROM CURRENT ALK OR INhibitor

ROSI INHIBITOR TREATMENT IN LUNG CANCER
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Background: ALK and ROSI kinase inhibitors have achieved tremendous success in the treatment of lung cancer patients. However, the emergence of drug resistance limits their long term clinical applications. The mechanisms of resistance often include gene amplification, acquired mutations, bypass signaling, and epithelial-mesenchymal transition (EMT). The bypass and EMT-based resistances constitute the majority of the resistant patient population, especially after multiple kinase inhibitor treatment. None of the current ALK or ROSI inhibitors can overcome bypass or EMT-based resistance when applied as a single agent therapy. SRC kinase has been identified to contribute broadly to cancer treatment resistance via participation in signaling pathways required for DNA synthesis, control of receptor turnover, actin cytoskeleton rearrangement, migration, adhesion, invasion, motility, and survival. SRC/FAK signaling plays important roles in regulating antitumor immunity, cancer stem-like properties, and EMT. Here we deployed a polypharmacology approach to combating multiple resistance mechanisms spontaneously.

Methods: Recombined enzyme assays, engineered cell lines and H2228 cells were used to evaluate TPX-0005 in vitro and in vivo models. Results: TPX-0005 is a potent ALK/ROS1/TRK inhibitor with a rigid three-dimensional macrocyclic structure and a much smaller size (MW <370) than current ALK/ROS1/TRK inhibitors. The compact structure allows TPX-0005 efficiently target the center of ATP binding site and be able to circumvent the steric interference from clinical resistant mutations. Therefore, TPX-0005 potently inhibited both wild type and mutant ALK/ROS1/TRK fusion proteins including gatekeeper and solvent front mutations at low nanomolar concentration. In addition to its primary targets, TPX-0005 is also a potent SRC/FAK inhibitor. H2228 lung cancer cell line, endogenously expressing EML4-ALKV3 protein, is refractory to crotzobin and cetiribin in cell proliferation assay (IC$_{50}$ ~1 μM). The upregulation of multiple RTKs including EGFR and IGF1R, as well as cancer stem cell marker CD44 in H2228 cells is believed to confer the primary resistance to selective ALK inhibitors. Inhibition of SRC/FAK kinases will modulate RTK expression and cancer stem-like properties to restore the sensitivity to ALK inhibitor. TPX-0005 inhibited the phosphorylation of EML4-ALK (IC$_{50}$ 13 NM), SRC and FAK (IC$_{50}$ S70-80 nm), along with other downstream signaling targets in H2228 cells. It leads to dependent-down regulation of EGFR and CD44 expression levels. As a result, TPX-0005 overcame the primary resistance and effectively inhibited cell proliferation (IC$_{50}$ 0.1 μM) and cell migration of H2228 cells. Conclusion: TPX-0005 exerts unprecedented polypharmacology profile for combating multiple resistance mechanisms including acquired mutations, bypass signaling, cancer stemness, and metastasis, that warrants further clinical investigation.

Keywords: ALK, ros1, Src, Resistance


P3.02A-010 EVALUATION OF ABBREVIATED ALK EXPRESSION IN LUNG CANCER BY RT-PCR AND COMPARISON WITH FISH AND IMMUNOHISTOCHEMISTRY
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Background: In advanced lung cancer patients the gold standard for detecting ALK gene rearrangements is fluorescence in situ hybridization (FISH), and ALK protein expression can be also evaluated by immunohistochemistry (IHC). A single analysis performed alone may not detect all the ALK-positive cases and some patients with discordant FISH and IHC respond to tyrosine kinase inhibitors (TKIs). In this study we evaluated ALK aberrant expression in surgical specimens by a reverse transcription (RT)-PCR, to investigate its clinical utility and its concordance with FISH and IHC. Methods: ALK aberrant expression was retrospectively investigated on RNA from formalin-fixed paraffin-embedded tissue (FFPET) of 24 advanced lung adenocarcinoma patients, previously evaluated by FISH and IHC. We used a one-step Scorpion RT-PCR that allows the mRNA reverse transcription and the cDNA amplification for ALK kinase-domain, normally not expressed, and a control gene, to assess RNA quality. Results: Results are reported in Table 1.

Conclusion: Despite the instability of mRNA from FFPET, only 2 samples resulted inadequate for RT-PCR. RT-PCR was in disagreement with both FISH and IHC in one case, which is likely to be a RT-PCR false positive. RT-PCR did not detect ALK aberrant expression in a FISH positive case, which was negative also by IHC; unfortunately, this patient died after a cycle of pemetrexed therapy, before undergoing a second line TKI treatment. The presence of ALK rearrangements does not necessarily imply increased protein levels. Therefore, the complex transcriptional and post-transcriptional regulations, so further analysis at RNA levels may clarify discrepancy between FISH and IHC allowing a better stratification of patients who could benefit from TKIs. Therefore, according to our results the RT-PCR evaluating ALK aberrant expression regardless of the fusion partners should be considered for introduction into routine ALK testing in lung cancer.

Keywords: one-step RT-PCR, aberrant expression, ALK
Abstracts

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POSTER SESSION 3 – P3.02A-012 PATIENT-REPORTED SYMPTOMS AND QUALITY OF LIFE (QOL) IN EAST ASIAN PATIENTS WITH ALK+ NSCLC TREATED WITH CRIZOTINIB VS CHEMOTHERAPY

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Background: The phase 3 study PROFILE 1012 is an ongoing phase 3 study of similar design (NCT01633901) conducted in an East Asian population in China, Hong Kong, Malaysia, Taiwan, and Thailand. Here, we present findings on patient-reported symptoms and QoL. Methods: Patients with previously untreated, ALK+ advanced NSCLC were randomized 1:1 (stratification: ECOG PS 0 or 1 vs 2) to crizotinib 250 mg PO BID or pemetrexed/carboplatin (PCC) in ALK+ NSCLC. Patients, who received crizotinib (n=103) had significantly longer median time to deterioration (TDD) for chest pain, dyspnea, or cough compared to PCC (n=98) (2.8 mo [95% CI: 1.4, 6.5] vs 0.3 mo [95% CI: 0.3, 0.5], respectively; HR=0.432 [95% CI: 0.307, 0.610]; P<0.0001). Crizotinib treatment, compared to PCC, was associated with a significantly greater change from baseline in global QoL and physical, role, cognitive, and social functioning (Table). QLQ-C30 results demonstrated that crizotinib-treated patients experienced either improvement or reduced worsening of most symptoms compared to PCC-treated patients. QLQ-LC13 data showed improvement or reduced worsening across all symptoms for crizotinib, relative to PCC.


Keywords: non-small cell lung cancer, quality of life, ALK+, crizotinib

POSTER SESSION 3 – P3.02A-013 BRIGATINIB IN CRIZOTINIB-REFRACTORY ALK+ NSCLC: CENTRAL ASSESSMENT AND UPDATES FROM ALTA, A PIVOTAL RANDBOMIZED PHASE 2 TRIAL


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Background: The phase 2/3 study ALTA assessed the efficacy and safety of brigatinib compared to crizotinib in patients with locally advanced or metastatic ALK+ NSCLC who had progressed on or after crizotinib treatment. Updated results from ALTA and other Phase 2 trials are presented. Methods: Patients with ALK+ NSCLC who had progressed on crizotinib were randomized 1:1 to receive brigatinib 100 mg PO daily or crizotinib 250 mg PO BID in a double-blind manner. The primary endpoint was objective response rate (ORR) in ALTA, as determined by independent central review. ORR was also assessed in other trials. Results: ORR were 28% and 11% for brigatinib and crizotinib, respectively. Brigatinib was well tolerated, with fewer adverse events (AEs) of grade 3 or 4 and fewer discontinuations due to AEs compared to crizotinib. Conclusion: Brigatinib significantly delayed time to treatment failure relative to crizotinib in patients with ALK+ NSCLC. The reduction in AEs of grade 3 or 4 with brigatinib compared to crizotinib is promising and is supported by other Phase 2 trials.

Keywords: non-small cell lung cancer, ALK+, brigatinib, crizotinib
Background: Brigatinib, an investigational next-generation ALK inhibitor, has yielded promising activity in crizotinib-treated ALK+ NSCLC patients in a phase 1/2 trial (NCT01449461). As responses and adverse events (AEs) varied with starting dose, two brigatinib regimens are under evaluation in ALTA (NCT02094573). Methods: Patients with crizotinib-refractory advanced ALK+ NSCLC were randomized 1:1 to receive brigatinib at 90 mg qd (arm A) or 180 mg qd with a 7-day lead-in at 90 mg (arm B) and stratified by presence of brain metastases at baseline and best response to prior crizotinib. Primary endpoint was investigator-assessed confirmed ORR per RECIST v1.1. Results: 222 patients were enrolled (arm A, n=112/arm B, n=110). Median age (A/B) was 51/57 years, 55%/58% were female, 74%/74% previously received chemotherapy, and 71%/67% had brain metastases. As of February 29, 2016, 64/112 (57%) patients in arm A and 76/110 (69%) patients in arm B were receiving brigatinib; median follow-up was 7.8/8.3 months. The Table shows investigator-assessed endpoints by arm and subgroup for select baseline characteristics. Independent review committee–assessed endpoints (A/B, n=112/110; as of May 16, 2016) confirmed ORR 48%/53%, median PFS 9.2/16.5 months. Any-grade treatment-emergent AEs (≥25% overall frequency; A/B, n=109/110 treated): nausea (33%/40%), diarrea (19%/38%), headache (28%/27%), cough (18%/34%); grade ≥3 events (excluding neoplasm progression; ≥3% frequency): hypertension (6%/6%), increased blood CKP (3%/9%), pneumonia (3%/5%), increased lipase (4%/3%). A subset of treatment-naïve patients (3%, grade ≥3) had therapy-related death (excluding neoplasm progression) (4/36 and 3/36 patients). A subset of patients (11%, grade ≥3); 7/14 patients were successfully retreated. No new class of toxicities was observed. Conclusion: In each arm, brigatinib yielded substantial responses and prolonged PFS, with an acceptable safety profile. 180 mg with 90 mg lead-in was not associated with increased pulmonary AEs with early onset (median onset: Day 2) compared with 90 mg, particularly with respect to PFS. 

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**POSTER SESSION 3 - P3.02A: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/IMMUNOTHERAPY ALK CLINICAL - WEDNESDAY, DECEMBER 7, 2016**

**P3.02A-014 PATIENT REPORTED GENERAL HEALTH STATUS IN A STUDY OF CRIZOTINIB VERSUS CHEMOTHERAPY IN PATIENTS WITH NON- SMALL CELL LUNG CANCER (NSCLC)**

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Background: Patients with advanced NSCLC typically experience symptoms compromising their quality of life (QoL), making this an important therapeutic goal. PROFILE 1029 (NCT01639001) is an ongoing open-label, Phase 3 study in East Asian patients with previously untreated, ALK+ advanced NSCLC in China, Hong Kong, Malaysia, Taiwan, and Thailand. Patient-reported health status outcomes are presented here. Methods: Patients were randomized with 1:1 (stratification: ECOG PS 0 or 1, 1) to crizotinib 250 mg PO BID or pemetrexed 500 mg/m² IV with either cisplatin 75 mg/m² or carboplatin (PCC) to achieve an AUC of 5–6 mg·min/mL, IV q3w for ≤6 cycles. Health status assessed using the EuroQoL 5D (EQ-5D) was a secondary endpoint of the study. The EQ-5D consists of a visual analogue scale (VAS) range from 0 (worst imaginable health state) to 100 (best imaginable health state) and a descriptive measure (no, some or extreme) of problems in 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, was to be completed at baseline and on day 1 of each cycle until treatment termination or withdrawal. The data were analyzed using a mixed model analysis. Results: The proportion of patients completing at least one question on the EQ-5D questionnaire ranged from 97.6% to 100% for crizotinib-treated patients over 42 cycles of treatment and from 98.0% to 100% for PCC-treated patients over a maximum of 6 cycles of treatment. The estimated overall change from baseline in the EQ-5D VAS was 3.429 (95% confidence interval [CI]1.20, 5.64) for crizotinib and 0.4927 (95% CI: -2.75, 1.77) for PCC. The difference between crizotinib and PCC was 3.9136 (95% CI: 0.85, 6.98; P<0.05). The estimated overall change from baseline in the EQ-5D utility score was 0.0502 (95% CI: 0.02, 0.08) for crizotinib and 0.0077 (95% CI: 0.02, 0.04) for PCC. The difference in utility score changes for crizotinib versus PCC was 0.0425 (95% CI: 0.00, 0.08; P<0.05). End of treatment descriptive results showed no deterioration from baseline across most EQ-5D dimensions. Conclusion: A statistically significantly (p-value ≤0.05) greater improvement from baseline in general health status (EQ-5D-VAS) and utility scores, was observed for crizotinib-treated patients compared with PCC-treated patients.

Keywords: ALK+, crizotinib, non-small cell lung cancer, quality of life

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**P3.02A-015 CERTITINIB AS FIRST-LINE THERAPY IN PATIENTS WITH ALK-ARRANGED NON-SMALL CELL LUNG CANCER: ASCEND-1 SUBGROUP ANALYSIS**

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Background: In the open-label, phase 1 ASCEND-1 study (NCT01283516), certitinib demonstrated durable whole body and intracranial responses in patients with ALK-rearranged (ALK+)-non small cell lung cancer (NSCLC) (Kim et al. Lancet Onc 2016). Median progression-free survival (PFS) was promising in ALK inhibitor (ALK-) naïve patients (18.4 months), most of whom had received one or more lines of chemotherapy. Here, efficacy and safety of certitinib are summarized in a subset of treatment-naïve patients enrolled in ASCEND-1. Methods: Patients with ALK+ NSCLC enrolled worldwide received certi tinib 750 mg/day (fasted). Median progression-free survival (PFS) was compared with the ALK inhibitor (ALK-) naïve patients enrolled in ASCEND-1. The median PFS was 11.1 months. Conclusion: Median progression-free survival (PFS) was comparable in ALK-rearranged (ALK+) patients with ALK-arranged (ALK-) patients enrolled in ASCEND-1. Keywords: ALK, ceritinib, NSCLC, TKI
five (31.3%) an ECOG performance status of 0, and all had stage IV disease. Median time from primary site diagnosis to ceritinib initiation (range) was 1.8 months (1.0-3.9). At data cut-off, median duration of exposure (range) was 4.5 months (2.5-5.4). Late onset median duration of follow-up (range) was 29.6 months (4.7–39.1). In these 16 treatment-naïve patients, per investigator assessment, the overall response rate was 68.8% (95% confidence interval [CI]: 41.3, 89.0) and the disease control rate was 87.5% (95% CI: 67.1, 98.2). Median duration of response was 21.1 months (95% CI: 5.5, 31.1). Median investigator-assessed PFS was 19.3 months (95% CI: 4.2, 26.3), and median overall survival was 39.1 months (95% CI: 19.1, 39.1). Among three patients with baseline brain metastases, one had brain metastases selected as target lesion and achieved a partial intracranial response. The most frequently reported any-grade adverse events (AEs), regardless of study drug relationship, were diarrhea (93.8%), nausea (81.3%), ALT or AST increase (each 81.3%), and vomiting (62.5%). AEs requiring intervention were predominantly managed with dose reduction/interruption. Overall, 13 patients (81.3%) discontinued treatment, due to disease progression (n=6), consent withdrawal (n=3), AEs (n=2), administrative problems or death (each n=1). Conclusion: Ceritinib demonstrated durable efficacy in treatment-naïve patients with ALK+ NSCLC. Safety was consistent with the overall ASCEND-1 study population. An ongoing, prospective, phase 3 study (ASCEND-4) in which patients are randomized to receive either ceritinib or chemotherapy will provide further evidence for the clinical benefit of ceritinib in previously untreated patients with ALK+ NSCLC.

Keywords: Ceritinib, treatment naïve, ALK+ NSCLC

P3.02A-016 POOLED EFFICACY AND SAFETY DATA FROM TWO PHASE II STUDIES (NP28673 AND NP28761) OF ALECTINIB IN ALK+ NON-SMALL-CELL LUNG CANCER (NSCLC)

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Background: Alectinib is an FDA-approved ALK TKI, for treatment of patients with ALK+ metastatic NSCLC who have progressed on, or are intolerant to, crizotinib. Systemic and CNS efficacy was demonstrated in two single-arm, phase II studies (NP28673 [NCT01801111] and NP28761 [NCT01871805]). We report the pooled systemic efficacy and safety analysis of alectinib from 2016 cut-offs 22 January, NP28761 and 1 February, NP28673. Methods: Patients were ≥18 years, had locally advanced or metastatic ALK+ NSCLC [FDA-approved FISH test] and had progressed on, or were intolerant to, crizotinib. Patients received oral alectinib 600mg twice daily until disease progression, death or withdrawal. The pooled analysis assessed objective response rate (ORR) by an independent review committee (IRC) using RECIST v1.1 (primary endpoint in both studies); disease control rate (DCR); duration of response (DOR); progression-free survival (PFS); overall survival (OS); and safety. Results: The pooled dataset included 225 patients, (n=138 NP28673; n=87 NP28761). Median age was 53 years, 60% of patients had baseline CNS metastases and 77% had received prior chemotherapy. The response-evaluable (RE) population by IRC included 189 patients (84%). Median follow-up was 18.8 months (0.6–29.7). In the RE population (n=189) ORR by IRC was 51.3% (95% CI 44.0–58.6); all partial responses, a DCR of 78.8% (95% CI 71.2–84.4), with a median DOR of 14.9 months (95% CI 11.1–20.4) after 58% of events. In patients with prior chemotherapy (n=148), IRC ORR was 49.3% (95% CI 41.0–57.7); DCR: 79.3% (95% CI 71.6–85.3), median DOR: 14.9 months (95% CI 11.1–21.3) after 58% of events. In patients with prior chemotherapy-naïve (n=41), IRC ORR was 58.5% (95% CI 42.1–73.7), DCR: 78.0% (95% CI 62.4–89.4); median DOR: 11.2 months (95% CI 8.0–NE) after 54% of events. In the total pooled population (n=225) median PFS by IRC was 8.3 months (95% CI 7.0–11.3) after 69% of events and median OS was 26.0 months (95% CI 21.4–NE) after 43% of events. Grade ≥3 adverse events (AEs) occurred in 40% of patients and the most common were dyspnea (4%), elevated levels of blood creatine phosphokinase (4%) and alanine aminotransferase (3%). The mean dose intensity was 94.6%. Fourteen patients withdrew due to AEs; 20.9% had AEs leading to dose interruptions/modification. Conclusion: This pooled analysis confirmed alectinib has robust systemic efficacy with a durable response in this population and in patients with or without prior chemotherapy. Alectinib had an acceptable safety profile.

Keywords: NSCLC, ALK-inhibitor, Alectinib, phase II pooled analysis

P3.02A-017 INDIRECT NAIVE COMPARISON OF POST-CRIZOTINIB TREATMENTS FOR ALK+ NON-SMALL-CELL LUNG CANCER (NSCLC)

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Background: Comparing the efficacy of ALK inhibitors in post-crizotinib therapy of ALK+ NSCLC is hampered by the lack of comparator ALK inhibitor treatment arms in pivotal studies. An indirect naive comparison was undertaken to explore study results for the investigational ALK inhibitor brigatinib and the currently available agents alectinib and ceritinib following progression on crizotinib. Baseline characteristics were examined to determine if the distribution of prognostic factors differed across studies, and outcomes were compared. Methods: Patient characteristics and study outcomes (objective response rate (ORR), progression-free survival (PFS), duration of response (DOR), and adverse events (AEs)) for alectinib, ceritinib, and brigatinib were extracted from pivotal study publications identified in a systematic literature review, alectinib prescribing information, and brigatinib data in post-crizotinib settings. Outcomes were compared over the longest follow-up reported. Results: All pivotal studies were multicenter and open label; populations were similar in median age, sex ratio, and baseline disease stage. Slight imbalances among studies exist in Eastern Cooperative Oncology Group/World Health Organization status and central nervous system metastases at baseline. DOR was numerically higher in the brigatinib phase 1/2 study for subjects receiving 180 mg once daily with 7-day lead-in at 90 mg versus other studies (Table). Median PFS and DOR were also higher in brigatinib studies versus alectinib and ceritinib studies; PFS 95% confidence intervals did not overlap between brigatinib and ceritinib studies. Rates of discontinuation due to AEs were similar across studies, but AE-related dose reductions were most frequent in ceritinib studies.

(See Table next page)
Conclusion: Pivotal trials for ALK inhibitors share many similarities, making an indirect comparison possible. Naive comparison suggests brigatinib may have a favorable efficacy profile compared with currently available therapies, while crizotinib may require dose reduction more frequently to manage AEs. Further analyses are needed to determine the magnitude and direction of potential bias.

Keywords: brigatinib, Ceritinib, non–Small-Cell Lung Cancer, Alectinib

**Table. Naïve Comparison of ALK+ NSCLC Patients Treated With Alectinib, Brigatinib, and Ceritinib After Crizotinib**

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<thead>
<tr>
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<th>Alectinib</th>
<th>Brigatinib</th>
<th>Ceritinib</th>
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<td>9.9</td>
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<td>8.3</td>
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<td>15248</td>
<td>11.1</td>
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<tr>
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<td>35.7</td>
<td>11.3</td>
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<td><strong>Median follow-up, months</strong></td>
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<td><strong>Median OS, months</strong></td>
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Keywords: Carcinoma, Non-Small-Cell Lung, Anaplastic lymphoma kinase, pemetrexed

**P3.02A-019 REAL WORLD UTILIZATION AND OUTCOMES OF ALK-POSITIVE CRIZOTINIB TREATED METASTATIC NSCLC PATIENTS IN US COMMUNITY ONCOLOGY PRACTICE**

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Background: It is estimated that 3-5% of non-small cell lung cancers (NSCLC) are ALK-positive. Crizotinib was the first approved ALK inhibitor for metastatic NSCLC, demonstrating efficacy in clinical trial settings. However, there is less data on the utilization and patient outcomes associated with crizotinib in real-world clinical practice. Objectives of this study consisted of describing demographic and disease characteristics, treatment patterns, and outcomes in US community practice. Methods: This was a retrospective, observational study of adult crizotinib-treated ALK-positive patients with metastatic NSCLC who received treatment between 9/1/2011 and 10/31/2014, from an observational database of patients treated in a US community oncology practice. Results: A total of 309 crizotinib patients were included in the analysis. Median age was 65 years (IQR 55-74). At study entry, 49% were female, 19% had performance status 0, and 41% had prior chemotherapy. Conclusion: Pemetrexed-based regimens may prolong progression free survival compared with other regimens in ALK positive NSCLC in the first line setting. Exposure to pemetrexed is associated with improved survival compared with that of pemetrexed-naïve controls in ALK positive NSCLC.

Keywords: Carcinoma, Non-Small-Cell Lung, Anaplastic lymphoma kinase, pemetrexed
P3.02A-020 CLINICAL FAILURE TO CRIZOTINIB IN PATIENTS WITH ANAPLASTIC LYMPHOMA KINASE-POSITIVE ADVANCED NON-SMALL-CELL LUNG CANCERS

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Background: Crizotinib, as the standard treatment for use in first-line treatment of anaplastic lymphoma kinase (ALK)-positive advanced non-small-cell lung cancer (NSCLC), showed superiority over platinum-based chemotherapy in advanced ALK-positive lung adenocarcinoma. Undoubtedly, the resistance to crizotinib is a current bottleneck which limits its clinical application. However, there are few reports about clinical failure to crizotinib, especially the correlation between the failure patterns of crizotinib and survival benefit. Methods: Totally, 171 ALK-positive NSCLC patients treated with crizotinib were reviewed at the Guangdong General Hospital in China from October 2010 to July 2016. The status of ALK rearrangement was assessed by Lysis ALK Break Apart fluorescence in situ hybridization, reverse transcription polymerase chain reaction, or Ventana ALK immunohistochemistry. Chi-square test and Kaplan-Meier survival curve were used to analyze the results statistically. Results: Among enrolled patients, 47.5% (81/171) gained secondary resistance, 10.5% (18/171) had primary resistance. Cox regression analysis showed that the primary resistance, ECOG performance status of 0 or 1, and ALK status had a significantly longer PFS2 time compared with those who did not (p=0.039). Multivariable Cox regression analysis showed that the PFS2 time with initial crizotinib therapy, the objective response rate (ORR) and median PFS time (PFS1) in the 33 patients studied were 63.6% and 8.6 months, respectively (Figure 1). Conclusion: Outcome endpoints were similar between groups, although potentially limited by small sample size. Results from this study are consistent with findings from clinical trials.

Keywords: real world utilization, patient outcomes, crizotinib, advanced NSCLC

Conclusion: This study provides further evidence of the benefit of continuing crizotinib therapy in Chinese patients with progressive ALK-positive NSCLC. Patients with a longer PFS1 and those who received local brain therapy had better survival with continued crizotinib therapy.
P3.02A-022 EXPERIENCES OF PATIENTS RECEIVING TREATMENT WITH CERITINIB TO TREAT ALK+ NON-_SMALL CELL LUNG CANCER: A QUALITATIVE STUDY
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Background: Ceritinib (Zykadia) is a recently approved second-line agent for anaplastic lymphoma kinase (ALK)+ non-small cell lung cancer (NSCLC). The current study sought to describe healthcare providers’ (HCPs) decisions to treat with ceritinib and to describe patient-reported side effects, perceived effectiveness and attitudes toward ceritinib. Methods: One-on-one telephone interviews were conducted with HCPs caring for patients treated with ceritinib using a semi-structured interview guide designed to explore treatment decision-making, adverse events (AEs) and their management. Patients with current or past experience of ceritinib completed semi-structured telephone interviews designed to capture their experience. A thematic analysis of interview transcripts was conducted using qualitative analysis software, MaxQDA. Results: Study participants comprised 10 HCPs (6 oncologists, 4 nurses) and 18 patients (9 female) aged 36-78 years (mean=51.0; SD=11.3). HCPs reported relying on two main factors when deciding to switch patients to ceritinib or to next-line treatment after ceritinib: evidence of sufficient clear-cut progression and poor tolerance to treatment. Four HCPs reported considering clinical trials or other newly approved drugs instead of ceritinib. Patients and HCPs concurred that the most frequently reported side effects of ceritinib include diarrhea (n=15 patients; n=9 HCPs), nausea (n=13; n=10), vomiting (n=12; n=6), and abdominal pain (n=10; n=7). Dose reduction, antiemetic and anti-diarrheal medications, and home remedies (e.g. ginger ale, crackers) were reported as being effective at managing these side effects prophylactically or once they occurred. Taking ceritinib with food was reported by 5 patients and 4 HCPs, and helped to improve nausea, vomiting or abdominal pain. Patients reported that ceritinib was effective in achieving or maintaining symptom control for cough (n=12 of 12 patients symptomatic at diagnosis) and shortness of breath (n=9 of 11 patients symptomatic at diagnosis). Of 11 patients with lung tumors at start of ceritinib, 13 reported positive tumor response during treatment. Three of 7 patients with brain metastases achieved reduction or no evidence of disease with ceritinib in combination with other interventions (e.g., radiation). Patients were asked about what they thought about ceritinib: tumor response and symptom control, an extension of life, or improvement in quality of life were key themes. Patient-reported dislikes included side effects and number of pills. Of 14 patients asked specifically, all stated the benefits of ceritinib outweigh its side effects. Conclusion: Patients perceived ceritinib as an effective treatment for ALK+ NSCLC, AEIs were reported to be manageable and patients were willing to manage these in order to experience the treatment benefits.

Keywords: Ceritinib, ALK+NSCLC, symptoms, qualitative

P3.02A-023 TREATMENT PATTERNS AND EARLY OUTCOMES OF ALK+ NON-SMALL CELL LUNG CANCER PATIENTS RECEIVING CERITINIB: A CHART REVIEW STUDY
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Background: Ceritinib is the first second-generation ALK inhibitor approved in the US to treat ALK+ non-small cell lung cancer (NSCLC) patients who progressed on or were intolerant to crizotinib. This study provides the first real-world description of the characteristics, treatment patterns, and early outcomes of ALK+ NSCLC patients who received ceritinib in clinical practice. Methods: From March to June 2016, 23 US oncologists provided data retrospectively from the medical charts of their adult patients diagnosed with locally-advanced or metastatic ALK+ NSCLC who received ceritinib following crizotinib therapy. Clinical characteristics, treatment patterns, and early outcomes on ceritinib were assessed. Best response on ceritinib was evaluated using RECIST criteria. Results: Participating oncologists reviewed charts of 58 ALK+ NSCLC patients treated with ceritinib. 46% of the patients were male, 52% were never smokers, and median age at ceritinib initiation was 63 years. Patients started ceritinib following a median of 10.6 months on crizotinib; 21% of patients had prior chemotherapy experience. At ceritinib initiation, many patients had multiple distant metastases, most commonly in the liver (60%), bone (53%), and brain (38%). While 71% initiated ceritinib at 750mg once daily, 19% received 600mg once daily, and 10% received 450mg once daily. 17% of patients were instructed to take ceritinib with food; 50% were instructed to fast. Median follow-up after ceritinib initiation was 3.8 months. Although follow-up was short, most patients achieved either a complete (8%) or partial (61%) response on ceritinib, regardless of metastatic site present at initiation (Table). Among the 21 patients who discontinued ceritinib, 6 received alecetinib, 2 chemotherapy, 2 immunotherapy, and 11 received no further anti-neoplastic therapy. Conclusion: These early findings of ceritinib use in clinical practice suggest that ceritinib is effective at treating crizotinib-experienced ALK+ NSCLC patients, regardless of the location of metastatic sites. Future studies with longer follow-up are warranted.

Keywords: non-small cell lung cancer, Anaplastic lymphoma kinase, Ceritinib, Best response

P3.02A-024 RESPONSE TO CRIZOTINIB IN A LUNG ADENOCARCINOMA PATIENT HARBORING EML4-ALK TRANSLOCATIONAL ADNEXAL METASTASIS
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Background: Lung cancer with ovarian metastasis or adnexal metastasis harboring anaplastic lymphoma kinase gene (ALK) translocation is rare. Crizotinib, a novel ALK tyrosine kinase inhibitor, has already shown an impressive single-agent activity in ALK-positive lung cancer. Methods: Our case is the first report of crizotinib effective for ALK-positive adenocarcinoma with adnexal metastasis. A 33-year-old woman was diagnosed with adnexal metastasis from non-small cell lung cancer (NSCLC). Histological examination of the tumors showed adenocarcinoma. The right lung biopsy tissue and left adnexal mass biopsy tissue were both revealed the presence of an ALK rearrangement by Ventana (DSF3) ALK immunohistochemistry (IHC) assay (Ventana Medical Systems, Roche, Inc). Results: The patient experienced a remarkable tumor response to crizotinib treatment.

Keywords: non-small cell lung cancer, Anaplastic lymphoma kinase, Ceritinib, Best response
Conclusion: Although the adnexal location is an uncommon metastasis site from lung cancer, oncologists should be aware of the possibility of such metastasis for female patients with ALK rearrangement NSCLC. Considering this remarkable response, we conclude that the presence of adnexal metastasis in NSCLC patients with ALK rearrangement should be attentive.

Keywords: Ovarian metastasis, non-small cell lung cancer, ALK, Crizotinib

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P3.02A-025 PROS WITH CERTITINIB VERSUS CHEMOTHERAPY IN PATIENTS WITH PREVIOUSLY UNINTERRUPTED ALK-ARRANGED NONSQUMOUS NSCLC (ASCEND-4)

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Background: Here, we present the patient-reported outcomes (PROs) of ceritinib versus chemotherapy as first-line treatment for advanced ALK+ NSCLC. Methods: Untreated, ALK+, advanced, nonsquamous NSCLC patients (N=376) were randomized (1:1) to ceritinib 750 mg/day (n=187) or chemotherapy (n=189); [pemetrexed 500 mg/m2 plus cisplatin 75 mg/m2 or carboplatin AUC 5-6] for 4 cycles followed by maintenance ceritinib. PROs were assessed using EORTC quality-of-life questionnaire (QLQ-C30), the lung cancer module (QLQ-LC13), Lung Cancer Symptom Scale (LCSS), and EQ-SD. Results: Median treatment exposure was 66.4 weeks for ceritinib and 26.9 weeks for chemotherapy. PRO compliance was high, ≥80% at most timepoints. Ceritinib significantly prolonged time to deterioration of lung cancer-specific symptoms (pain, dyspnea, and cough) versus chemotherapy in both LCSS and QLQ-LC13 instruments (composite endpoints for LCSs, HR=0.61 [0.41, 0.90]; and QLQ-LC13, HR=0.48 [0.30, 0.71]) months (Table). In the QLQ-C30 instrument, 4 of 5 functional domains and 6 of 9 symptom scales improved with ceritinib (%P<0.05; 2 scales related to gastrointestinal symptoms indicated deterioration for ceritinib. In agreement with most other scales showing symptom improvement, ceritinib demonstrated significant improvements in Global Health Status/Qol in the same instrument (QLQ-C30, P<0.001) as well as for EQ-SD-SL index (P<0.001) and EQ-SD-SL VAS (P<0.05 from cycle 13 until 49).

Conclusion: Untreated ALK+ NSCLC patients experienced significantly greater improvements in lung cancer-specific symptoms on treatment with ceritinib. General health status was significantly improved with ceritinib versus chemotherapy. Overall, PRO results from all 4 instruments independently showed improvements highlighting the consistency and robustness of these findings.

Keywords: QOL, Ceritinib, ALK, Phase 3

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P3.02A-026 CRIZOTINIB IN CLINICAL PRACTICE AND IN CLINICAL TRIALS - HOW MUCH THE RESULTS DIFFER?

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Background: In Slovakia, since October 2012, crizotinib has been available for the treatment of adults with previously treated ALK-positive advanced NSCLC based on the therapeutic indication approved by the European Medicines Agency. The purpose of this study was to assess the results achieved with crizotinib in the treatment of NSCLC in clinical practice in Slovakia, and to compare them with the results from the key clinical trial PROFILE 1007. Methods: In the multicentre retrospective study, approved by the Ethical Committee of the Specialised Hospital of St Zorazdus Zobar, the data of 34 ALK-positive patients from 8 centres were reviewed. Data regarding ALK testing and results were obtained from the central laboratory database (Comenius University Jesenius Medical Faculty and Martin’s Biospy Centre). Data regarding patients were obtained from the databases of participating institutions and patient files. Fluorescence in situ hybridisation (FISH) with break-apart probes was used for the confirmation of ALK rearrangement in all cases. Response to treatment was evaluated using RECIST criteria v. 1.3. Statistical analyses were performed using MedCalc software. PFS and OS
were estimated using the Kaplan–Meier method. Results: Between October 2012 and December 2015, 34 ALK-positive patients with locally advanced or metastatic NSCLC were treated with crizotinib, 31 of them after the first-line chemotherapy. Characteristics of patients: median age, years (range): 58 (23–77), eCOG/WHO PS: 0, 1, 2, 3 in 1, 2, 3, 6, and 4 patients, respectively. Histology: adenocarcinoma in 33 cases, NSCLC, NOS in one. Patients with locally advanced disease: 2, with metastatic disease: 32. Median PFS was 18 months (95%CI: 13–22), median OS (number of events: 13, 39.24%): 32 months (95%CI: 18–32), response rates: CR + PR: 11, 23.65%, (95%CI 0–50%), SD: 2, 7.15%, PD: 20, 8.8%, not stated. 1. There was a significant improvement in PFS within 2 months, mean difference: -0.62, p = 0.005. Grade 3/4 toxicities occurred in 15/2 patients. Crizotinib was permanently discontinued due to AEs in 2 patients only. PFS and OS in our study were numerically better in comparison with previous 107. On the other hand, common grade 3 toxicities occurred also more often. Conclusion: Our study provides real-world evidence of the efficacy of crizotinib in patients with ALK-positive NSCLC, treated outside of clinical trials.

Keywords: crizotinib, response, survival, NSCLC

**POSTER SESSION 3 – P03.02a: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/IMMUNOTHERAPY ALK CLINICAL WEDNESDAY, DECEMBER 7, 2016**

**P03.02a-07 RETROSPECTIVE ANALYSIS OF THE EFFECTIVENESS AND SAFETY OF ALK INHIBITORS IN ALK-POSITIVE LUNG CANCER PATIENTS**

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**Background:** Patients with non-small cell lung cancer (NSCLC) harboring ALK rearrangements have been shown to exhibit a good response to ALK-inhibitor treatment. However, serious adverse events are observed in some patients. Therefore, it is important to precisely evaluate severity of adverse events and treat properly. Methods: We performed a retrospective study of the efficacy and safety of ALK inhibitors in ALK-positive lung cancer patients. Between September 2013 and April 2016, 9 patients receiving ALK inhibitors in our department were analyzed. All patients gave informed consent for the use of their clinical data. Results: The median age was 67 years (range, 54.2–94 years), and the histological type of cancer was adenocarcinoma in all cases. One patient had stage IIB, four patients had stage IV and four patients had postoperative recurrence. Seven cases were fluorescence in situ hybridization (FISH) positive/immunohistochemistry (IHC) positive, and two cases were FISH positive/IHC negative. Crizotinib and alectinib were administered orally and determined the expression of thymidylate synthetase (TS) to provide a reference. Drug discontinuation rate because of adverse events was higher in crizotinib treatment than in alectinib treatment (71% vs 50%). No treatment-related death occurred. Conclusion: Although ALK inhibitors have therapeutic efficacy and safety of ALK inhibitors in ALK-positive lung cancer patients. Therefore, it is important to precisely evaluate severity of adverse events and treat properly. Presented results are consistent with the published literature. Keywords: Non-small cell lung cancer, Adenocarcinoma, Anaplastic lymphoma kinase, Crizotinib

**POSTER SESSION 3 – P03.02a: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/IMMUNOTHERAPY ROSI – WEDNESDAY, DECEMBER 7, 2016**

**P03.02a-09 PATIENTS WITH ROSI RERANGEMENT POSITIVE NON-SMALL CELL LUNG CANCER BENEFIT FROM PEMETREXED-BASED CHEMOTHERAPY**

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**Background:** ROSI gene rearrangement in non-small cell lung cancer (NSCLC) patients has recently been identified as a driver gene and benefited from crizotinib treatment. However, no data is available for ROSI-positive NSCLC about chemotherapeutic options and prognostic data. We investigated pemetrexed-based treatment efficacy in ROSI translocation NSCLC patients and determined the expression of thymidylate synthase (TS) to provide a rationale for the efficacy results. Methods: We determined the ROSI status of 1750 patients with lung adenocarcinoma. Patients’ clinical and therapeutic profile were assessed. In positive cases, thymidylate synthetase (TS) mRNA level was performed by RT-PCR. For comparison, we evaluated the TS mRNA status and pemetrexed-based treatment efficacy from 170 NSCLC patients with anaplastic lymphoma kinase (ALK) translocation, 1.5 years, 56 years, 60.7% of patients were women, and 71.4% were never-smokers. Twenty (94.2%) were adenocarcinomas. All patients were EGFR negative. Twenty (76.9%) were stage IV. Fifteen patients (57.7%) were treated in first line with pemetrexed chemotheraphy (CT), thirteen of them received OS. The most frequent treatment-related adverse events were emesis (G1) vision disorders (G1), and increased AST/ALT (G3). Three patients treated with CT had grade 3 toxicity (pneumonia with respiratory failure, anemia, peripheral neuropathy). Median follow-up of study population was 13.5 months. In patients treated with crizotinib objective response rate (ORR = complete response + partial response) was 50% and clinical benefit (CB = complete response + partial response + stable disease) was 75%. In patients treated with CT ORR was 6.7% and CB was 73%. Seven (26.9%) patients died during the study period. Median overall survival has not been reached. Conclusion: ALK directed therapy, namely crizotinib, was safe and well-tolerated. Most of the patients (91.7%) were treated with the standard dose of 250mg twice per day. One patient needed dose reduction due to hepatotoxicity (G3, CTCAE V4). The most frequent treatment-related adverse events were emesis (G1) vision disorders (G1), and increased AST/ALT (G3). Three patients treated with CT had grade 3 toxicity (pneumonia with respiratory failure, anemia, peripheral neuropathy). Median follow-up of study population was 13.5 months. In patients treated with crizotinib objective response rate (ORR = complete response + partial response) was 50% and clinical benefit (CB = complete response + partial response + stable disease) was 75%. In patients treated with CT ORR was 6.7% and CB was 73%. Seven (26.9%) patients died during the study period. Median overall survival has not been reached. Conclusion: ALK directed therapy provided increased benefit and lower toxicity compared to CT. During the study period, there were several treatment guidelines updates impacting the patient’s management. Presented results are consistent with the published literature. Keywords: Non-small cell lung cancer, Adenocarcinoma, Anaplastic lymphoma kinase, Crizotinib

**POSTER SESSION 3 – P03.02a: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/IMMUNOTHERAPY ROSI – WEDNESDAY, DECEMBER 7, 2016**

**P03.02a-02 ANAPLASTIC LYMPHOMA KINASE FUSION ONCOGENE POSITIVE NON-SMALL CELL LUNG CANCER – THE EXPERIENCE OF AN INSTITUTION**

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**Background:** Approximately 3–7% of lung tumors harbor Anaplastic Lymphoma Kinase (ALK) fusions. The aim of the current study was to characterize the population of patients with ALK positive non small cell lung cancer (NSCLc) treated in our Institution. Methods: Retrospective analysis of 26 ALK positive NSCLc, diagnosed between December/2008 and February/2016. Eligible patients had lung adenocarcinoma harboring ALK translocation according to fluorescence in situ hybridization. Best response was assessed using RECIST (version 1.1). Results: Twenty-one patient cases are reported, diagnosed between 2008 and 2016. Median age was 56 years, 60.7% of patients were women, and 71.4% were never-smokers. Twenty (94.2%) were adenocarcinomas. All patients were EGFR negative. Twenty (76.9%) were stage IV. Fifteen patients (57.7%) were treated in first line with pemetrexed chemotherapy (CT), thirteen of them received OS. The most frequent treatment-related adverse events were emesis (G1) vision disorders (G1), and increased AST/ALT (G3). Three patients treated with CT had grade 3 toxicity (pneumonia with respiratory failure, anemia, peripheral neuropathy). Median follow-up of study population was 13.5 months. In patients treated with crizotinib objective response rate (ORR = complete response + partial response) was 50% and clinical benefit (CB = complete response + partial response + stable disease) was 75%. In patients treated with CT ORR was 6.7% and CB was 73%. Seven (26.9%) patients died during the study period. Median overall survival has not been reached. Conclusion: ALK directed therapy provided increased benefit and lower toxicity compared to CT. During the study period, there were several treatment guidelines updates impacting the patient’s management. Presented results are consistent with the published literature. Keywords: Non-small cell lung cancer, Adenocarcinoma, Anaplastic lymphoma kinase, Crizotinib
translocation lung adenocarcinoma may benefit from pemetrexed-based chemotherapy. TS mRNA level enables the selection of therapeutic options for ROS1 translocation patients.

Keywords: Thymidylate synthetase, ROS1, pemetrexed, efficacy

POSTER SESSION 3 - P.02A: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/IMMUNOTHERAPY
RSO1 – WEDNESDAY, DECEMBER 7, 2016

P.02A-030 ROS1 FUSION CHINESE LUNG ADENOCARCINOMA PATIENTS TREATED WITH CRIZOTINIB DETECTED USING NEXT-GENERATION GENOTYPING FROM CTDNA
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Background: Chromosomal rearrangements involving the c-ros oncogene 1 (ROS1) have been described as a subset of non-small cell lung cancer (NSCLC). Recently Crizotinib has exhibited marked therapeutic efficacy in the treatment of the ROS1 fusion NSCLC. However, resistance often occurs and repeated biopsy is necessary for tumor genotyping and underlying resistant mechanism. Circulating tumor DNA (ctDNA) represents a promising way to assess tumor genetic profile non-invasively. This study aims to whether liquid biopsies accurately screen disease diagnosis and reflect the response to Crizotinib treatment through analysis of ctDNA for ROS1 fusions in patients with lung adenocarcinoma, and to elucidate the underlying mechanisms of ROS1 target acquired resistance. Methods: Twelve plasma samples were collected from a cohort of 4 patients with ROS1 fusion advanced stage lung adenocarcinoma, confirmed by fluorescent in situ hybridization (FISH) in tissue. A prospective retrospective analysis on ctDNA was further performed from archived plasma samples using our ctDNA panel with concurrent CT or MRI imaging at the baseline and 8-week intervals during responsive Crizotinib treatment, and at progressive disease. Results: All patients showed detectable levels of ROS1 fusion in ctDNA at baseline. Upon treatment with Crizotinib, response rate is inversely correlated with levels of ROS1 fusion. One patient with progressive disease, patient 1, exhibited a detectable CD74-ROS1 fusion with 13.5% concentration at baseline; it was undetectable at partial response and re-elevated to 8.2% accompanied by an acquired G2032R mutation when disease progressed. Conclusion: Our ctDNA panel could be applied clinically to detect ROS1 fusion from plasma for accurate screening and convenient monitoring where detection correlates with disease status, and could distinguish mutations associated with Crizotinib induced resistance in patients with NSCLC, thus facilitating personalized cancer therapy.

Keywords: lung adenocarcinoma, ROS1 fusion, crizotinib, circulating tumor DNA (ctDNA)

POSTER SESSION 3 - P.02A: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/IMMUNOTHERAPY
RSO1 – WEDNESDAY, DECEMBER 7, 2016

P.02A-031 NON-SMALL CELL LUNG CANCER TARGETED THERAPY IN CASE OF ROS1 REARRANGEMENT
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Background: ROS1 gene rearrangement refers to rare genetic aberrations, occurs in 1-2% of patients with NSCLC. Of ROS1 rearrangement patient This subgroup of patients is high sensitive to crizotinib therapy. Methods: Clinical case: Patient, male, 87 y.o., observed in our clinic since July, 2013. Diagnosis: Lung adenocarcinoma, metastasis in the both lungs, pleura, supra- and subclavicular lymph nodes, bones, T3N3M1b, stage IV. EGFR «-», ALK «-». Concomitant diseases: Ischemic heart disease. The heart rhythm disorder (ventricular and supraventricular extrasystole). Treatment performed: 1st line—Alimta + carboplatin x6 cycles (July - November 2013). Partial response. Disease progression in September 2014. Chemotherapy was proceeded according to the previous regimen. After 4 cycles in February 2015 the further progression of disease was observed. Biopsy of axillary lymph node was performed. Molecular testing found ROS1 gene rearrangement. On 02.04.2015 crizotinib was started with dose reduction 250 mg/day. The next day bradycardia (cardiac rate 39 beats per minute) developed, QTc was prolonged to 558 msec (initially 470 msec). Crizotinib administration was stopped. Development of this adverse event as a rule is the cause of withdrawal of crizotinib. However, high probability of targeted therapy response and absence of alternative in choosing of antineoplastic therapy made us use all the opportunities for correction of adverse events.

10.04.2015 implantation of dual chamber pacemaker was performed and crizotinib 250 mg/day administration was proceeded. The patient’s condition was satisfactory, there were no other adverse events and dose of crizotinib was increased to the standard level 625 mg/day. Results: In 7 weeks after beginning of targeted therapy (28.05.2015) PET-CT was performed - local areas of abnormal uptake of FDG were not detected. The patient continues crizotinib at the current time – last PET-CT was done 04.07.2016. Complete response remains. The duration of response is 15 months.

Conclusion: Therefore, we pronounced the early and durable response.

Keywords: ROS1 gene rearrangement, crizotinib
50% had partial response as the best response to first-line treatment. The objective response rate was 53%, stable disease 26.5%, disease progression 16.3%, non-evaluable 4% and disease control rate of 79.6%. The combination had an adequate tolerance, mostly toxicities grades 1-2. Toxicities grade 3 or 4 were mainly fatigue (14%), diarrhea (13%), hyporexia (7%), neutropenia (7%), nausea (6%), vomiting (1%). Nintedanib dose was reduced in 27 patients (27%). The median duration of the treatment with nintedanib was 6.7 months. Conclusion: Overestimated responses may be related to the retrospective desing of the study and due to that were valued by investigator which could influence the results. The Safety of nintedanib in real-life patients was demonstrated and not very different from the results in the LUME Lung 1 trial. Gastrointestinal toxicity were the most frequent side effects, mostly toxicities grades 1-2.

Keywords: Metastatic NSCLC, nintedanib, second line treatment, compassionate-use program in Mexico

**POSTER SESSION 3 - P3.02A: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/IMMUNOTHERAPY MISCELLANEOUS - WEDNESDAY, DECEMBER 7, 2016**

**P3.02A-033 THE HUMANISTIC BURDEN ASSOCIATED WITH CARING FOR ADVANCED NSCLC PATIENTS IN EUROPE - A REAL WORLD SURVEY OF CAREGIVERS**

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Background: While the financial aspects of the burden on caregivers for patients with advanced Non-Small Cell Lung Cancer (aNSCLC) have been examined, limited data on burden associated with humanistic issues exists. The aim of this study was to estimate the humanistic burden incurred by these caregivers. Methods: Data were taken from a multi-center, cross-sectional study of aNSCLC patients and their caregivers conducted in France, Germany and Italy. The study consisted of three components: medical chart review, patient questionnaire and caregiver questionnaire. Overall, 683 consulting patients and 277 accompanying informal caregivers were recruited via treating physicians. The impact on health related quality of life was measured using the EuroQol-5D (EQ-5D-3L) while caregiver burden was measured using the Zarit Burden Interview (ZBI), which consists of 22 items, each rated 0-4. ZBI scores were grouped into: little/no burden (0-20), mild/moderate (21-40), moderate/severe (41-60) and severe burden (61-88). Scores of 24+ were assumed to identify caregivers at risk of depression. Results: Caregivers’ mean (SD) age was 55.2 years (19.6), and 57% were female. The median duration of the treatment with nintedanib was 6.7 months. Differences in ZBI were observed between carers of 1st line and 2nd line advanced cancer (18.5). Caregivers for aNSCLC patients suffer significant humanistic burden in addition to the overall burden faced by patients and is likely to result in additional costs. When assessing the impact of a treatment, the potential to improve the impact on caregivers should also be included.

Keywords: Metastatic NSCLC, humanistic burden, caregiver burden

**P3.02A-034 VEMURAFENIB IN PATIENTS WITH NON-SMALL CELL LUNG CANCER (NSCLC) HARBORING BRAF MUTATION. PRELIMINARY RESULTS OF THE ACSÉ TRIAL**

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Background: BRAF is found mutated in 2-3% of stage IV NSCLC. BRAF inhibitors have been reported to have antitumor activity. A nationwide access to vemurafenib for cancer patients with tumors presenting with BRAF mutations was launched by the French National Cancer Institute (INCa) providing free access to tumor molecular diagnosis. The ACSÉ-Vemurafenib study is the 2nd exploratory multi-tumor 2-stage design phase II trial of ACSé program. We report the preliminary results on the NSCLC cohort in this nationwide program. Methods: BRAF mutational status was assessed on InCa molecular genetic platforms by either direct sequencing or NGS. Patients with BRAF mutation including BRAF V600E and others less common mutations, progressing after at least one standard treatment (including a platinum-based doublet, unless pts were considered as unfit for chemotherapy) were proposed to receive vemurafenib 960 mg BID. Responses were centrally assessed using RECIST v1.1 every 8 weeks. Results: From Oct. 13, 2014 to June 15, 2016, 65 patients were enrolled including 55 NSCLC harboring BRAF V600E and 10 mutations with other activating BRAF V600E NSCLC patients evaluable for the best overall response (BOR) with a minimum follow-up of 15 months, 15 PR, 8 SD, 10 PD, 5 deaths before assessment and 1 missing were observed. The objective response rate was 38.3% [95% CI:23.4-55.4], and the disease control rate 59% [42.7-74.4]. Median duration of response was 5 months [1.9-2.1]. Progression-free survival (PFS) at 4 months was 48.2% [31.8-62.8]. No response was reported among the 7 evaluable patients with other BRAF mutations with 5 PD, 1 death before assessment and 1 missing as BOR; PFS at 4 months was 14.3% (0.7-46.5). 18 patients were still on treatment at the cut-off date. 4/7 have stopped vemurafenib (25 PD, 15 AEs, 1 death, 1 doctor's decision, 5 patient's decisions). Conclusion: Vemurafenib provided response rate and DCR in BRAF V600E pretreated NSCLC but was not found efficient in NSCLC with other BRAF mutations. These results underline the interest of integrating BRAF V600E in biomarkers routine screening.

Keywords: BRAF mutation, Vemurafenib, NSCLC, AcSé

**P3.02A-035 CAN AIRWAY STENTING AVOID SUFFOCATION DEATHS CAUSED BY MALIGANT AIRWAY OBSTRUCTION?**

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Background: Airway stenting is undoubtedly the mainstay procedure for coughing patients suffering from airway obstruction. Suffocation death is the most painful ending for those patients. The impact of airway stent treatment to avoid this tragic event was investigated. Methods: Between 2000 and 2014, 57 patients underwent airway stenting to avoid life-threatening airway symptoms. Results: There were no in-hospital deaths. An improvement of airway symptoms was achieved in 54 patients (94.7%) and the median survival after stenting was 3.7 months. At death, only 8 (14%) of those patients died due to direct airway symptoms, including respiratory difficulty, even when their general condition was good (Suffocation death group).

Keywords: Suffocation death, airway stenting

**POSTER SESSION 3 - P3.02A: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/IMMUNOTHERAPY MISCELLANEOUS - WEDNESDAY, DECEMBER 7, 2016**

**P3.02A-036 CAN AIRWAY STENTING AVOID SUFFOCATION DEATHS CAUSED BY MALIGANT AIRWAY OBSTRUCTION?**

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Background: Airway stenting is undoubtedly the mainstay procedure for coughing patients suffering from airway obstruction. Suffocation death is the most painful ending for those patients. The impact of airway stent treatment to avoid this tragic event was investigated. Methods: Between 2000 and 2014, 57 patients underwent airway stenting to avoid life-threatening airway symptoms. Results: There were no in-hospital deaths. An improvement of airway symptoms was achieved in 54 patients (94.7%) and the median survival after stenting was 3.7 months. At death, only 8 (14%) of those patients died due to direct airway symptoms, including respiratory difficulty, even when their general condition was good (Suffocation death group).
Conversely, the other 49 patients mostly died due to systemic cancer spread, but all 49 cases had no pain associated with airway symptoms. Therefore, suffocation death appears to have been avoided in those 49 (85.9%) patients (Non-suffocation death group). In a univariate analysis, “Stenosis at mid trachea” was the most problematic factor when attempting to obtain some benefit from stenting and this may be due to the difficulty of achieving accurate stent (mainly straight silicon stent) fixation in such lesions.

Keywords: suffocation, airway stent

**POSTER SESSION 3 – P.02A: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/IMMUNOTHERAPY MISCELLANEOUS – WEDNESDAY, DECEMBER 7, 2016**

**P.02A-036 PHASE 1 STUDY OF CERITINIB 450 MG OR 600 MG TAKEN WITH A LOW-FAT MEAL VERSUS 750 MG IN FASTED STATE IN ALK+ METASTATIC NSCLC**

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Background: The anaplastic lymphoma kinase (ALK) inhibitor ceritinib is approved at 750 mg fasted for the treatment of patients with ALK-rearranged (ALK+) metastatic non-small cell lung cancer (NSCLC) pretreated with crizotinib. The pharmacokinetic (PK) part of this study (Part 1) compares PK exposure of ceritinib following food consumption versus a fasted state in advanced ALK+ NSCLC patients. Methods: Part 1 of this prospective, open-label, multicenter, randomized, 3-arm, phase 1 study (ASCEND-8; NCT02299505) is investigating PK and safety of ceritinib in advanced ALK+ NSCLC patients, treatment-naive or pretreated with multiple lines of chemotherapy and/or crizotinib. Here, we compare steady-state PK of ceritinib 450 mg or 600 mg taken with a low fat meal versus ceritinib 750 mg fasted (primary endpoint) and report preliminary safety outcomes from Part 1. Part 2 continues to randomize treatment-naive patients and will assess safety and efficacy. Results: As of June 16, 2016 (data cut-off), 137 patients were randomized in a 1:1:1 ratio to each treatment arm; 135 patients received one dose (safety set) and 97 patients had evaluable steady-state PK data. Disease characteristics were comparable between arms. Median follow-up duration was 4.4 months (range, 0.1–13.9). Relative to 750 mg fasted, the 450 mg fed arm demonstrated comparable steady-state PK, while the 600 mg fed arm showed ~25% higher steady-state PK (Table). Preliminary safety data suggests overall frequency of AEs and types of AEs were comparable between arms. However, incidences of gastrointestinal (GI)-related AEs (diarrhea, nausea or vomiting) were lowest, with no grade 3/4 GI AEs reported, in the 450 mg fed arm.

Conclusion: Steady-state PK was comparable in advanced ALK+ NSCLC patients taking ceritinib 450 mg with a low-fat meal versus 750 mg fasted. This study continues to enroll treatment-naive patients into Part 2 to assess efficacy across the three treatment arms and assess longer safety follow-up.

Keywords: Ceritinib, ALK, NSCLC

**P.028-001 PHASE 1 DOSE ESCALATION OF PF-06747775 (EGFR-T790M INHIBITOR) IN PATIENTS WITH ADVANCED EGFRM (DEL 19 OR L858R+/T790M) NSCLC**

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Background: PF-06747775 (PF-7775) is a highly potent, selective third generation irreversible EGFR-TKI, effective against EGFR-TKI sensitizing and resistance (T790M) mutations in NSCLC cell lines; IC50s between 3-12 nM and 26X greater selectivity toward mutant vs. wild-type (WT) EGFR. This is the first report from an ongoing Phase 1, first in human multicenter study (NCT02349633) of PF-7775 in patients with metastatic EGFRm+ NSCLC. Methods: EGFRm+ NSCLC pts, with acquired resistance to EGFR-TKIs enrolled into dose escalation cohorts of PF-7775, orally once daily, beginning at 25 mg. Stable brain metastases were allowed. All pts were assessed for pharmacokinetics (PK), response to therapy, and adverse events (AEs). Prospective central 1730M testing was optional for dose escalation cohorts, but is required in subsequent expansion cohorts. Plasma samples were collected from all patients for ctDNA analysis of EGFR mutations. Results: Dose escalation is complete. 26 patients enrolled in 7 dose levels (25-600 mg): 58% female, mean age 63.5 years, Asian/Caucasian 6/34%, 14/25 1730M+. Dosing reached 600 mg and then was expanded at alower dose for better long term tolerability. RECIST responses were observed at all dose levels. BOR is PR (42.3%, 5 1730M+), stable disease 623.1%, 4 1730M+, PD 2(7.7%, 1 1730M+), symptomatic deterioration 1(3.8%; 1 T790M+), and indeterminate 6(23.1%; 3 T790M+). The AE profile is very favorable as predicted from the large WT margin. No DLTs were observed. Grade 3 AEs were noted at >150 mg (diarrhea [n=4, 15.4%], skin toxicities [n=8, 30.8%]). Figure 1. Best Change from Baseline in Tumor Size (%

PK were generally dose-proportional at doses of 25-600 mg, with a median apparent t1/2 of 6 (range 4-30). Conclusion: PF-7775 has demonstrated early signals of clinical activity and is well tolerated in EGFRm+ NSCLC pts with acquired resistance to EGFR-TKIs.

Keywords: EGFRm NSCLC, 1790M, Targeted therapy, 3rd generation EGFR TKI
Background: Although superior clinical benefits of first-line epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) in the treatment of advanced non-small-cell lung cancer (NSCLC) has been reported with different sensitivity. The sensitivity of second-line TKIs in NSCLC patients with different genotypes was unknown. The purpose of this study is to investigate the clinical outcome of NSCLC patients with and without brain metastases in different EGFR tumor genotypes receiving EGFR-TKIs as a second-line treatment. Methods: The treatment outcomes of 166 NSCLC patients harboring either the exon 19 deletion or the L858R point mutation of EGFR treated by second-line TKIs were retrospectively reviewed. Results: The disease control rate (DCR) and objective response rate (DOR) of enrolled NSCLC patients were 77.7% and 11.4%, respectively. The exon 19 deletion group had a significantly longer median progression-free survival (PFS) (6.7 vs. 4.5 months, P=0.002) and overall survival (OS) (13.7 vs. 11.7 months, P=0.002) compared with the L858R mutation group for NSCLC patients, as well for patients with brain metastasis (PFS: 6.7 vs. 3.9 months, p<0.001), OS: (13.7 vs. 7.9 months, p=0.006). The median PFS and OS for NSCLC patients with bone metastases were 4.8 months (95% CI, 4.0-5.6 months) and 12.9 months (95% CI, 8.7-17.1 months), respectively. No significant difference was observed for patients with brain metastasis for different mutations. EGFR genotype and EOGC PS were independent predictors of PFS for both NSCLC patients with and without brain metastasis. No smoking (P=0.001), exon 19 deletion (P=0.03), EGOC PS (0-1) (P=0.001) and no brain metastasis (P=0.002) were correlated with longer OS for all NSCLC patients. For patients with brain metastasis, age at disease progression (P=0.009), genotype (P=0.02) and EGOC PS (P=0.001) were independent predictors of OS. For patients with bone metastasis, EGOC PS (P=0.001) was an independent predictor for both PFS and OS. Female (P=0.01), even smoking (P=0.05), number of brain metastases (P=0.03) and EGOC PS (P=0.02) were related to a longer PFS. EGFC PS (0-1) (P=0.001) was associated with a longer OS. Rash, fatigue, and anorexia were the three most frequent side effects observed. No significant side effects difference between exon 19 and 21 mutation groups were observed. Conclusion: NSCLC patients harboring exon 19 deletion achieved better PFS and OS than those with L858R mutation, indicating that EGFR mutations are significant prognostic factors for advanced NSCLC patients with and without brain metastasis receiving second-line EGFR-TKIs treatment.

Keywords: Epidermal growth factor receptor, Tyrosine kinase inhibitors, Brain metastasis, Non-small-cell lung cancer

P.3.028-002 TREATMENT OUTCOME COMPARISON BETWEEN EXON 19 AND 21 EGFR MUTATIONS AFTER SECOND-LINE TKIS IN ADVANCED NSCLC PATIENTS
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Background: The second line treatment of the EGFR – mutation in advanced NSCLC patients with and without brain metastasis, Non-small-cell lung cancer patients with and without brain metastasis receiving second-line EGFR-TKIs were observed. Conclusion: NSCLC patients harboring exon 19 deletion experienced more fatigue, and anorexia were the three most frequent side effects observed No significant interaction between treatment arms and VeriStrat classification. Conclusion: Despite comprehensive, multifaceted analysis, no biomarkers were identified that predict treatment benefit with afatinib compared to patients with SCC of the lung. Afatinib is a treatment option in this setting irrespective of patients’ tumour genetics or EGFR expression levels. However, patient outcome strongly depends on VeriStrat status.

Keywords: Squamous cell carcinoma of the lung, NSCLC, afatinib

P.3.028-004 EGFR MUTATION IN SQUAMOUS CELL ADVANCED NSCLC IN PERSAHABATAN HOSPITAL, JAKARTA INDONESIA
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Background: Tyrosine kinase domain gene mutations of the epidermal growth factor receptor gene (EGFR) have proven to be clinically significant in nonsmall-cell lung cancer (NSCLC), particularly in adenocarcinoma. However, EGFR mutations in other type of lung cancer such as squamous cell lung cancer is uncommon. Methods: This is a preliminary study of which EGFR mutations were more prevalent in Southwest Asia using immunohistochemistry (IHC) and immunohistochemistry (IHC) and Immunohistochemistry Melting (HRM) polymerase chain reaction (PCR) from cytologic samples of squamous cell lung cancer. Cytological samples were obtained from bronchoscopy or transthoracic needle biopsy. Trained lung pathologist determined the cytologic type of the tumor as squamous cell lung cancer. Immunohistochemical evaluation were not done since the cytological sample were limited. Results: Twenty subjects had confirmed squamous cell lung cancer were enrolled between June 2014-December 2014 in Pulmonary Referral Hospital/Persahabatan Hospital Jakarta Indonesia, of which 18(90%) were male, age between 50-75 years old. Eighty percent of subjects has stage IV/metastasis with Performance Status of 2.3 at the time of diagnosis. EGFR mutations were detected in 4 of 20 subjects (20%). Two subjects harbour exon 19 deletion, and 2 subjects harbour L858R mutation. Conclusion: These results suggest that EGFR mutations are found in 20% cytologically confirmed squamous cell lung cancer in this group.
Background: Patients with non-small-cell lung cancer (NSCLC) carrying specific mutations at epidermal growth factor receptor (EGFR) gene are usually sensitive to treatments with tyrosine kinase inhibitors (TKIs). However, not all EGFR-mutated NSCLC patients show a treatment response, and approximately 20-30% show primary resistance. Although the mechanisms responsible for acquired resistance are known, those responsible for primary resistance are not completely understood. In this study we aimed to assess the role of TP53 mutations in a cohort of advanced NSCLCs patients receiving first-line TKIs. We analyzed TP53 gene status in relation to outcome in terms of overall response rate, disease control rate (DCR), response duration, progression free survival (PFS) and overall survival (OS). Methods: We retrospectively analyzed 136 patients with advanced EGFR-mutated NSCLC treated with first-line TKIs from January 2012 to April 2015. Exons 5-8 of TP53 gene were amplified by PCR and sequenced by direct sequencing on 123 patients. DCR was defined as the sum of complete response, partial response and stable disease. The survival endpoints examined were PFS and OS. PFS was defined as the time from start of first-line treatment to disease progression or death, whichever occurred first. OS was defined as the time from start of first-line treatment to death. Results: TP53 mutations were observed in 37 (30.1%) patients: 10 (27.0%), 6 (16.2%), 9 (24.3%) and 12 (32.4%) in exons 5, 6, 7 and 8, respectively. DCR was 70% in TP53-mutated patients compared to 88% in TP53-wt patients (relative risk, RR = 0.39; 95% CI 1.21-8.48, p = 0.059). In particular, a 4-fold decrease was observed in patients with TP53 exon 8 mutation compared to 87% in exon 8 wt patients (RR 9.67 [2.71-36.63], p < 0.001). Shorter median PFS and OS were observed in patients with TP53 exon 8 mutations compared to other patients (4.2 months vs 12.5 months [p = 0.058] and 16.2 months vs 32.3 months [p = 0.0114], respectively); these differences became significant in the subgroup of patients with EGFR exon 19 deletion (4.2 months vs 16.8 months [p = 0.001] and 7.6 months vs not reached [p = 0.006], respectively), hazard ratio (HR) 6.99 (95% CI 2.34-20.87, p = 0.001) and HR 4.75 (95% CI 3.16-26.25, p = 0.013), respectively. Conclusion: TP53 mutations, in particular exon 8 mutations and those defined as non-disruptive, reduce responsiveness to TKI treatment and induce a worse prognosis in EGFR-mutated NSCLC patients, especially in those carrying exon 19 deletions.

Keywords: TP53, EGFR, Resistance, TKIs
EGFR-tyrosine kinase inhibitors (TKIs), about 50% carry malignancies. Among advanced NSCLC patients with an acquired resistance to holds promise as a non-invasive methodology for tumor monitoring in solid T790M was present in the 8 control cases (specificity of 100%). Of four patients who sensitivity of d-PCR in plasma versus tissue was 71.4%. No EGFR-3D, life technologies) in longitudinally (at baseline, at 4, 8, 12, 180, T790M remains unclear. We hypothesized that detecting the T790M developed. Four patients had L858R those with EGFR-19 deletion and T790M was frequently detected when new lesions were showed a PD before of 12 months compared to lower OS (14.6 versus 6.7 months, HR 1.47; 95% CI 0.85-2.53; p=0.165), but not significantly associated with VS status (p=0.656). At the multivariate analysis, CgA, HGF and VEGF were independently associated with VS Poor status. When clinical variables were also included (histology and PS), multivariate analysis evidenced VS Poor as the only independent prognostic biomarker associated with the VS Poor classification (p=0.0013). Plasma HGF levels (HR 2.083; 95% CI 1.306-3.321; p=0.0021) and tumor PD-L1 expression (HR 2.579; 95% CI 1.036-6.421; p=0.0417) remained independent prognostic biomarkers for shorter PFS. Conclusion: Inflammation and angiogenesis appear to be associated with the complex processes at the base of the VeriStrat signature. Plasma HGF levels and tumor tissue PD-L1 are prognostic in terms of a worse VS, but VeriStrat remains the only highly reproducible clinically relevant biomarker associated with OS. Y Gregor et al, The Lancet Oncology, p713, 15(7), 2014.

Keywords: NSCLC, VeriStrat, EGFR-TKIs

### P3.02B-008 QUANTIFICATION AND MONITORING OF TREATMENT RESPONSE IN EGFR MUTANT NSCLC PATIENTS BY DIGITAL-PCR IN PLASMA CFTDNA

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Background: The identification of activating epidermal growth factor receptor (EGFR) mutation is essential for deciding therapy in non-small cell lung cancer (NSCLC) patients. Circulating cell-free tumor DNA (cfDNA) holds promise as a non-invasive methodology for tumor monitoring in solid malignancies. Among advanced NSCLC patients with an acquired resistance to EGFR-typic kinase inhibitors (TKIs), about 50% carry T790M mutation, but its frequency in EGFR-TKI-nave patients and dynamic change during therapy remains unclear. We hypothesized that EGFR-mutation analysis detection in cfDNA for NSCLC may be feasible for monitoring treatment response to EGFR-TKIs and also predict drug resistance. Methods: EGFR sensitive mutations and T790M were analyzed using digital PCR (d-PCR) (Quantum studio 3D, life technologies) in longitudinal samples at baseline, at 4, 8, 12, 180, 270, 360 days) collected plasma samples (n=50) from 8 tissue-confirmed EGFR-mutant NSCLC patients treated with an EGFR-TKI (Gefitinib N = 4; Erlotinib N = 1; Afatinib N = 3). DNA extracted from plasma of 8 healthy blood donors were used to detect the specificity of EGFR mutant assay. Tumor assessment was performed according to RECIST criteria 1.1 every two months. Results: The sensitivity of d-PCR in plasma versus tissue was 71.4%. No EGFR mutation was present in the 8 control cases (specificity of 100%). Of four patients who developed progression disease (PD), in the samples of progression, T790M was detected in 75% of cases. The frequency of 790M in pre-TKI plasma samples was of 37.5%. EGFR sensitive mutations decreased at PD while T790M mutation increased in 75% of patients. Patients with concomitant pre-TKI EGFR 19 deletion and T790M showed a PD before of 12 months compared to those with L858R. T790M was frequently detected when new lesions were developed. Four patients had T790M level decreased to undetectable level with longer PFS than those with detectable T790M in blood. Conclusion: Our results indicated that d-PCR was a highly sensitive and useful method for detecting the T790M mutation. Moreover, dynamically monitoring T790M change might help determining EGFR-TKI resistance. We thank Italian Association for Cancer Research (AIRC) for supporting the study.

Keywords: cfDNA, advanced NSCLC, digital PCR, resistance to EGFR-TKIs

### P3.02B-010 URINE DETECTION OF EGFR T790M MUTATION IN NON- SMALL-CELL LUNG CANCER: AN OUTCOMES AND TOTAL COST OF CARE ANALYSIS

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Background: Third-generation tyrosine kinase inhibitors (3rd-TKIs) have proven effective in patients with EGFR T790M who progress on prior EGFR TKI therapy. Median progression-free survival (PFS) on a 3rd-TKI was 9-10 months for T790M+ patients compared to 2-4 months for T790M- patients. PFS is similar regardless of use of this specimen used to test T790M (tumor tissue, blood, or plasma). When using simulation analytics, the primary study aim was to assess the cost effectiveness of a urine-testing strategy (UTS) versus a tissue-testing strategy (TTS) for T790M detection in patients with EGFR positive lung adenocarcinoma and progression on prior TKI therapy.

Methods: Analytics followed International Society for Pharmacoecomics and Outcomes Research (ISPOR) and Society for Medical Decision Making (SMDM) guidelines for Good Modeling Practices, and Consolidated Health Economic Evaluation Reporting Standards (CHEERS) for reporting findings. Outcomes and economic implications were assessed from the perspective of a third-party US payer, stratified by government versus commercial fee schedules, and available adjustments for fees in commercial markets. A state-transition analysis and Markov model tracked patients from stable disease, progression, and to death. Full univariate and multivariate sensitivity analyses were performed to assess the robustness of findings and factors that most influenced outcomes and costs. Results:
Abstracts

Median PFS after treatment with 3rd-TKI was 3.4 months if tumor testing was T790M-versus 9.7 months if T790M+. Because urine testing can be used in patients for whom biopsy cannot be performed or when tissue testing reveals indeterminate results, PFS and OS were slightly increased using the UT. UTs resulted in avoidance of a biopsy procedure, potential complications, and tissue-based molecular testing in approximately 48% of patients, leading to a 2- to 10-fold total cost savings relative to the unit cost for a urine test. Within the robust variations in input parameters, the cost of a biopsy procedure including tissue-based and molecular testing were the most influential factors. Conclusion: UTs is a dominant scenario to TTS by saving costs and improving patient experience (e.g., PFS/OS, and reduction in biopsy related complications). This result is based on LEVEL I evidence from a large, randomized trial that showed PFS is similar among patients regardless of urine versus tissue testing for T790M mutation status.

Keywords: NSCLC, T790M, liquid biopsy, Health Economics

P.3.028-011 COMPARISON OF FOUR LEADING TECHNOLOGIES FOR DETECTING EGFR MUTATIONS IN CIRCUITING TUMOR DNA FROM PATIENTS WITH NON-SMALL CELL LUNG CARCINOMA

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Background: This study aimed to assess the ability of different technology platforms to detect epidermal growth factor receptor (EGFR) mutations including L858R, Ex19-del, T790M, and GT9X from circulating tumor DNA (ctDNA) in patients with non-small cell lung cancer (NSCLC). Methods: Plasma samples were collected from 20 patients with NSCLC including detailed clinical information along with data regarding treatment response. ctDNA was extracted from 10 mL plasma using the QiAamp Circulating Nucleic Acid Kit (Qiagen). Extracted ctDNA was analyzed using two real time-amplification refractory mutation system-quantitative PCR platforms (cobas\textsuperscript{®} EGFR Mutation Test: cobas; and AmoyDx\textsuperscript{®} EGFR 29 Mutations Detection Kit: Adx), one digital platform (Droplet Digital\textsuperscript{®} PCR, ddPCR: Bio-rad), and one next-generation sequencing platform (firefly NGS: Accuragen). Results: If a positive result was obtained from any one of the four platforms, the sample was categorized as positive. We identified 15 EGFR mutations in 20 patients with NSCLC using the four platforms, for which 7, 11, 10, and 12 mutations were detected by Adx, cobas, ddPCR, and firefly NGS, respectively. Among the 15 EGFR mutations, six and seven EGFR alterations demonstrated an allele frequency of more or less than 1% (group A or B, respectively), and two exhibited unknown allele frequency. In group A, 5, 5, 5, and 6 EGFR mutations were detected and the positive coincidence rate of any two platforms ranged from 66.7% to 100% and the kappa value varied from 0.787 to 1.000 in group A. In group B, 1, 5, 5, and 6 EGFR mutations were detected and the positive coincidence rate of any two platforms ranged from 16.7% to 100% and the kappa value varied from 0.270 to 1.000. The output of cobas, ddPCR, and firefly NGS uncovered 73, 69, 70, and 68 EGFR wild-type loci, respectively. The concordance and negative coincidence rates between any two platforms were over 90%. Conclusion: The detection rate and concordance were probably affected by the abundance of EGFR mutations and the sensitivity of different platforms. Three platforms, including cobas, ddPCR, and firefly NGS, exhibited higher positive coincidence and detection rates when the allele frequency was lower than 1%.

Keywords: Non-small-cell lung cancer, Epidermal growth factor receptor, Circulating Tumor DNA, next-generation sequencing

P.3.028-012 LONGITUDINAL MONITORING OF CTDNA EGFR MUTATION BURDEN FROM URINE CORRELATES WITH PATIENT RESPONSE TO EGFR TKI: A CASE SERIES

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Background: Circulating tumor DNA (ctDNA) are short DNA fragments released into the systemic circulation by rapid cell turnover, and excreted into the urine. Urinary ctDNA-based detection of oncogenic mutations is a non-invasive modality that can help in clinical decision making, especially when tissue biopsies are not available. When conventional imaging modalities are inconclusive, quantitative assessment of systemic ctDNA burden has the potential to assess response to therapy. In this case series we assessed EGFR mutation status at baseline and at intervals following administration of tyrosine kinase inhibitor (TKI) therapy to determine whether EGFR mutation load correlated with disease burden and therapeutic response. Methods: Four patients on anti-EGFR (TKI) were prospectively monitored for quantitative assessment of systemic mutant allele burden of activating and resistance EGFR mutations (Exon 19 deletions, L858R and T790M) in urine. EGFR mutations were quantitatively interrogated by short footprint mutation enrichment PCR followed by next-generation sequencing assays. Systemic mutant allele burden was compared to assessment of tumor burden computed by standard imaging modalities. Results: Patients 1, 2, and 3 were originally diagnosed with EGFR-positive NSCLC. Targeted molecular testing of systemic urine ctDNA revealed high EGFR mutation burden and the presence of the T790M resistance mutation at the time of progression on TKI therapy (550 copies/10\textsuperscript{6} genome equivalents (EQg)). Interestingly, the extent of radiographic progression in patient 3 was not completely clear, and urinary T790M along with clinical assessment of pain helped determine progression prior to obtaining radiographic confirmation. After initiation of a 3rd generation TKI (patient 1: ASP8273, patients 2 and 3: osimertinib), all patients experienced an appreciable decrease in the EGFR mutation burden, which was consistent with clinical improvement prior to radiographic imaging. Patient 4 presented with multiple lung nodules at diagnosis and a high systemic L858R mutant allele burden (550 copies/10\textsuperscript{6} EQg). Two months after initiation of first-line TKI, the main lesion and lymph nodes slightly improved, but the lung nodules progressed. The high systemic L858R burden persisted at the same level as pre-therapy. Conclusion: Urinary ctDNA-based quantitative assessment of systemic EGFR mutant allele burden is a non-invasive molecular diagnostic testing modality that correlates with tumor burden and response to therapy.

Keywords: ctDNA (circulating tumor DNA), Monitoring, tyrosine kinase inhibitor (TKI)

P.3.028-013 EVALUATION OF LUNG SPECIFIC GPA SCORE IN ADENOCARCINOMA PATIENTS WITH BRAIN METASTASIS AND EGFR ACTIVATING MUTATION

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Background: The lung specific GPA score is an index, commonly used for patients with non-small cell lung cancer (NSCLC) and brain metastasis (BM) in order to predict overall survival (OS) with the help of four easy-to-use items: age at the diagnosis of the brain metastasis; Karnofsky Performance Status (KPS), presence of extra cranial metastasis (ECM) and number of brain metastasis (Sperduto PW et al. J Clin Oncol 2012; 30:4925). However, this tool might not be appropriate to patients harboring EGFR activating mutations, which are known to have better prognosis than those with no activating mutations. The goal of our study was to determine if the Lung specific GPA score is adapted to population with these mutations. Methods: We retrospectively analyzed 108 Caucasians patients diagnosed with NSCLC between 2000 and 2014. Clinical features, systemic treatments (chemotherapy or EGFR tyrosine kinase inhibitors) and local brain treatment
Protein tyrosine kinase inhibitors (TKIs) in EGFR mutant patients (p). Recently, 3rd generation inhibitors (T790M) have demonstrated activity in EGFR mutant (mu) patients with AR to TKIs harboring T790M. Serum and plasma have been used as an alternative to tissue to detect both sensitizing EGFRm and T790M. We evaluated if (1) T790M could be monitored along T790Mi therapy in p with baseline T790M in serum, (2) T790M loss could be correlated to clinical and radiographic response, and (3) T790M disappears soon in rapid responders. Methods: 10 p out of a total of 15 T790M+p treated with T790Mi were selected according the baseline T790M+ in serum. Baseline characteristics, data on changes in T790M in serum; and radiographic and symptom changes along T790Mi therapy were collected. T790Mi in serum was detected using a PNA-locked nucleic PCR clamp-based technique. T790M was evaluated at baseline and at certain times after T790Mi initiation. Results: 80% of the p were female and never smoker; 100% were adenocarcinoma, Caucasian, del19, and had a PS 1 in 70% of the cases. 5 p were evaluable for response with 2 SD (r1-6), 40% had a rebiopsy for T790M evaluation, had 3 metastatic sites (r1-6), of 11.25 months (mo) [range (r)1-19 mo]. P received 2 previous treatments with first generation TKIs, with a median (m) time to treatment failure of 11.25 months (m) [range (r)1-19 mo]. P received 2 previous treatments with first generation TKIs, with a median (m) time to treatment failure of 11.25 months (m) [range (r)1-19 mo]. P received 2 previous treatments with first generation TKIs, with a median (m) time to treatment failure of 11.25 months (m) [range (r)1-19 mo]. P received 2 previous treatments with first generation TKIs, with a median (m) time to treatment failure of 11.25 months (m) [range (r)1-19 mo]. P received 2 previous treatments with first generation TKIs, with a median (m) time to treatment failure of 11.25 months (m) [range (r)1-19 mo]. P received 2 previous treatments with first generation TKIs, with a median (m) time to treatment failure of 11.25 months (m) [range (r)1-19 mo]. P received 2 previous treatments with first generation TKIs, with a median (m) time to treatment failure of 11.25 months (m) [range (r)1-19 mo]. P received 2 previous treatments with first generation TKIs, with a median (m) time to treatment failure of 11.25 months (m) [range (r)1-19 mo]. P received 2 previous treatments with first generation TKIs, with a median (m) time to treatment failure of 11.25 months (m) [range (r)1-19 mo]. P received 2 previous treatments with first generation TKIs, with a median (m) time to treatment failure of 11.25 months (m) [range (r)1-19 mo]. P received 2 previous treatments with first generation TKIs, with a median (m) time to treatment failure of 11.25 months (m) [range (r)1-19 mo]. P received 2 previous treatments with first generation TKIs, with a median (m) time to treatment failure of 11.25 months (m) [range (r)1-19 mo]. P received 2 previous treatments with first generation TKIs, with a median (m) time to treatment failure of 11.25 months (m) [range (r)1-19 mo]. P received 2 previous treatments with first generation TKIs, with a median (m) time to treatment failure of 11.25 months (m) [range (r)1-19 mo]. P received 2 previous treatments with first generation TKIs, with a median (m) time to treatment failure of 11.25 months (m) [range (r)1-19 mo]. P received 2 previous treatments with first generation TKIs, with a median (m) time to treatment failure of 11.25 months (m) [range (r)1-19 mo]. P received 2 previous treatments with first generation TKIs, with a median (m) time to treatment failure of 11.25 months (m) [range (r)1-19 mo]. P received 2 previous treatments with first generation TKIs, with a median (m) time to treatment failure of 11.25 months (m) [range (r)1-19 mo]. P received 2 previous treatments with first generation TKIs, with a median (m) time to treatment failure of 11.25 months (m) [range (r)1-19 mo]. P received 2 previous treatments with first generation TKIs, with a median (m) time to treatment failure of 11.25 months (m) [range (r)1-19 mo]. P received 2 previous treatments with first generation TKIs, with a median (m) time to treatment failure of 11.25 months (m) [range (r)1-19 mo].
was extracted from the tumor and their matched normal material. The paired-end whole exome sequencing (WES) of DNA was performed on the Illumina HiSeq 2500 sequencing platform. Results: Totally, five patients exhibiting primary resistance to EGFR-TKIs were enrolled and each was randomly matched with one patient possessing TKI sensitivity (Table1). The mean depth of the WES was 100x. The mean number of non-synonymous SNV per sample was 195 (range 97 to 348) in TKI-resistant group versus 84 (range 60 to 101) in TKI-sensitive group (P=0.059). Consistent with the initial result of Sanger sequencing, all 10 patients were found with EGFR sensitizing mutations (exon 19 deletions or L858R point mutation in exon 21), but no T790M mutation; the resistance group present with a lower EGFR mutant allele frequency than the sensitive group. Next generation sequencing of TKI-resistant specimens detected KRAS amplification (CN_{tumor}/CN_{normal} = 2.6) in one of five patients, and MET amplification (CN_{tumor}/CN_{normal} = 2.3) in another one. The recurrent mutation genes included FAT4, RBM10, TANC2, ACAN, PPFI2A, UBR4, XIRP2 and PRAMEF1.

Conclusion: Next-generation sequencing offers more complete genomic analysis to understand the mechanism of differential responses to EGFR-TKIs, which can lead to more precision therapy. KRAS amplification appears to be a newly mechanism underlying primary resistance to EGFR-TKIs in patients harboring TKI-sensitive EGFR mutations. However, it needs to be validated in a larger cohort.

Keywords: Non-small-cell lung cancer, Primary resistance, EGFR-TKIs

POSTER SESSION 3 - P3.02B: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/ IMMUNOTHERAPY EGFR BIOMARKERS - WEDNESDAY, DECEMBER 7, 2016

P3.02B-017 SEQUENCE OF EGFR-TKI TREATMENT AND BIM DELETION POLYMORPHISM AFFECT THE OUTCOME OF TREATMENT IN EGFR POSITIVE NSCLC

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Background: Bcl-2-like protein 11 (BIM) is a key protein in promoting apoptosis. BIM deletion polymorphism has been proposed as the intrinsic EGFR-TKI resistance and to predict poor response to EGFR-TKI treatment. However, there were conflict results of BIM deletion as the predictive biomarker in previous studies and EGFR-TKI reimbursement is a problem in most low and middle income countries. This study evaluated sequence of EGFR-TKI therapy and role of BIM deletion to maximize the cost-effectiveness of treatment in Thai population. Methods: Advanced EGFR-positive NSCLC patients were identified from database between 9/2012 and 12/2014. Retrospective review of 185 medical records was performed. Only 139 patients received EGFR-TKI. Archive tissues were available 129 samples. RT-PCR amplification designed to detect BIM deletion (2903 bp) in intron 2. The recurrent mutation genes included FAT4, RBM10, TANC2, ACAN, PPFI2A, UBR4, XIRP2 and PRAMEF1.

Conclusion: BIM deletion polymorphism could be one of the predictive biomarker to maximize the benefit of EGFR-TKI treatment. Furthermore, LBSR patients have longer survival if received EGFR-TKI as the first-line treatment. These results could help the low and middle income countries to maximize the cost-effectiveness and to solve reimbursement problem of EGFR-TKI therapy.

Keywords: BIM deletion polymorphism, Advance NSCLC, EGFR-TKI, Sequence of EGFR-TKI

POSTER SESSION 3 - P3.02B: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/ IMMUNOTHERAPY EGFR BIOMARKERS - WEDNESDAY, DECEMBER 7, 2016

P3.02B-018 DETECTION OF EPIDEMIC GROWTH FACTOR RECEPTOR MUTATIONS IN CIRCULATING CELL-FREE DNA VERSUS TUMOR BIOPSY

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Background: Epidermal growth factor receptor (EGFR) mutations are predictive marker of EGFR-tyrosine kinase inhibitor (TKI) therapy. We compared the sensitivity of EGFR mutation detection techniques between matched tumor tissue and peripheral blood sample in patients with lung adenocarcinoma. Methods: We collected the paired samples from plasma and paraffin-embedded tumor tissue in 202 patients before EGFR-TKIs. DNA extraction was performed using the QiAamp MinElute virus spin kit and EGFR mutation analysis was done by two detection methods. One is the PNAClamp™ which is the PNA-based PCR clamping that selectively amplifies only the mutated target DNA sequence as minor portion in mixture with the major wild type DNA sequences. The other is the PANAMutyper™ EGFR kit, which use PNA clamping-assisted fluorescence melting curve analysis to perform mutation detection and genotyping. The degree of agreement was evaluated by Cohen’s kappa value. Results: The EGFR mutation rates by PANAMutyper™ and PNAClamp™ were 51.0% vs. 47.0% in tissue, and 22.2% vs. 17.4% in plasma sample, respectively. Overall concordance rates were 77.7% vs. 79.9% in tissue and 22.2% vs. 17.4% in plasma sample, respectively. Overall concordance rates and the degree of agreement between tissue and plasma samples was better in PANAMutyper™ (kappa: 0.799 vs. 0.793) than PNAClamp™ (kappa: 0.783 vs. 0.781). Sensitivity of plasma EGFR mutations was higher (41.7% vs. 22.2%, p<0.001) and false negative rate was lower in PANAMutyper™ (5.2%) unlike PNAClamp™ (12.0%).

Conclusion: The sensitivity and concordance rate of PANAMutyper™ test were better than standard PNAClamp™ test. So this technique can be useful to detect EGFR mutation in circulating cell-free DNA sample.

Keywords: Sensitivity, EGFR mutations, cell-free DNA
Background: Several studies have shown that overexpression of thyroid transcription factor (TTF-1) may be associated with the presence of epidermal growth factor receptor (EGFR) gene mutations and predict survival in patients with non-small cell lung cancer (NSCLC). Nevertheless, the potential significance of TTF-1 immunostaining as a predictor of response to EGFR tyrosine kinase inhibitors (TKIs) has received limited research attention thus far. The aim of this study was to further explore the potential association between TTF-1 immunohistochemical expression and response to EGFR TKIs in patients with lung adenocarcinoma. Methods: The medical records of 129 patients with stage IV lung adenocarcinoma, treated at the Oncology Unit of Sotiria Athens General Hospital between January 2011 and December 2014, were retrospectively reviewed. All patients had treatment with EGFR TKIs (erlotinib or gefitinib) and had a known TTF-1 immunohistochemical expression status in formalin-fixed, paraffin-embedded tumour tissue. Demographic and clinicopathological features (age, gender, smoking status and performance status) and EGFR mutation status results were correlated to each other as well as with the response rate (RR) to EGFR TKIs, using univariate and multivariate variable regression analysis. Results: Median age of our study population was 68 years (range 26-88 years), while the majority were male (79/129 cases, 61.2%). Patients with EGFR mutant tumors had significantly higher response rates to EGFR TKIs compared to patients with wild-type EGFR tumors (p<0.001). TTF-1 positive staining was weakly associated with the presence of EGFR mutations, without reaching the level of statistical significance (p=0.053). Most importantly, TTF-1 positive staining was not significantly correlated with RR to EGFR TKIs, when gender, age, smoking status, EGFR mutation status and PS were included in the multivariate model. Conclusion: The present results failed to demonstrate any independent association between TTF-1 overexpression and the RR to EGFR TKIs in patients with advanced-stage lung adenocarcinoma. Prospective data from larger cohorts of patients are needed to clarify the exact predictive value of TTF-1 immunostaining in this setting.

Keywords: Epidermal growth factor receptor (EGFR), lung adenocarcinoma, response rate, thyroid transcription factor (TTF-1)
naive cases as well as those who developed clinical resistance to tyrosine kinase inhibitors. The later cases were examined for previous known and new T790M mutations using highly sensitive Droplet Digital PCR. Where ever feasible the results were compared to the secondary biopsy findings, duration of development of new T790M mutation and its serial plasma quantification results. Results: 20 Treatment naïve biopsy positive DEL19/L858R cases were tested for cell free DNA. All cases were positive with values ranging from 0.4% to 24%. 19 cases were checked for primary and secondary mutations on progression of disease. 12 cases showed secondary mutation along with the primary mutation. The values of T790M mutation ranged from 0.04% to 4.5%. We also had 3 cases with biopsy and cell free correlation of secondary mutation. None of them correlated. Conclusion: Droplet digital PCR is a robust platform to detect the primary driver EGFR mutations and can be used as a substitute/addendum to biopsy for initiating early treatment. It also appears to be too sensitive for detection of secondary T790M mutations. However response to treatment in patients with minimal cell free T790M values in plasma may need to be further investigated for clinical utilization of this platform.

Keywords: T790M, EGFR, droplet digital PCR, cell free DNA

P3.02B-023 PHYSICIAN PATTERNS OF CARE IN PATIENTS WITH EGFR MUTATION+ NSCLC: AN INTERNATIONAL SURVEY INTO TESTING AND TREATMENT CHOICE

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Background: (Applied for Late-Breaking Abstract Status) IASLC guidelines recommend EGFR mutation testing should be performed at diagnosis of advanced NSCLC to guide treatment decisions. In 2015 an international survey concluded that not all patients were tested or received test results before treatment initiation. This varied between countries and across regions. The aim of a follow-up survey in 2016 was to assess testing rates and HCP treatment choice in advanced NSCLC to identify improvements and changes compared to 2015. Methods: Online survey of 707 oncologists in 11 countries (Canada, China, France, Germany, Italy, Japan, South Korea, Spain, Taiwan, UK, USA) between July - August 2016. China was newly added in 2016. For better comparison with 2015 results, China was excluded from the primary results focus Results: Globally*, physicians requested EGFR mutation testing prior to first-line therapy of stage IIB/V NSCLC in 80% of patients. However, 18% of ordered tests were not received prior to deciding first-line therapy; an improvement on 2015 with 23%. Excluding histology, the main reasons for not testing prior to first-line therapy were insufficient tissue, poor performance focus Results

P3.02B-025 RAPID AND HIGHLY SENSITIVE EGFRDELEX19 AND KRAS EXON 2 MUTATION DETECTION IN EBUS-TBNA SPECIMEN OF LUNG ADENOCARCINOMA

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Background: First-line treatment with afatinib prolongs overall survival in patients with metastatic non-small-cell lung cancer (NSCLC) harboring EGFR exon 19 deletion mutations. Conversely, somatic KRAS mutations are negative predictors for benefit from EGFR-targeting agents. Rapid availability of these biomarker results is mandatory to prevent delayed or inferior treatments. Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is well-established for lung cancer diagnosis and staging. Next generation sequencing (NGS) via targeted resequencing allows simultaneous interrogation for multiple mutations, but has its limitations
based on the amount of tumor tissue required and assay times. RT-PCR using Light-Cycler technology (LC-RT-PCR) is a rapid and sensitive assay to detect somatic mutations in various tissues from NSCLC patients. The study’s aim was to analyze LC-RT-PCR is feasible for rapid EGFRdelEx19 and KRAS Exon 2 mutation detection in EBUS-TBNA samples and to compare results with results obtained via standard NGS mutation analyses. Methods: 48 surplus EBUS-TBNA samples (38 lymph nodes, 10 primary tumor) from 47 patients with pulmonary adenocarcinoma were analyzed. Two samples were collected per lymph node. One was used for routine cytology; the other was freshly frozen (ff). DNA from ff-biopsies was extracted using Genomic DNA buffer set (Qiagen, Germany). Mutation analysis by LC-RT-PCR was conducted as previously described. NGS was performed on MiSeq (Illumina) via targeted resequencing using a customized multiplex-PCR panel covering 36 exons from 11 genes. Mutations were annotated with a minimum frequency of 2%. Processing time was approximately 4 days for NGS and 2 hours for LC-RT-PCR analyses. Results: NGS of EBUS-TBNA samples was technically feasible for both markers in 22 (46%) samples, for EGFR testing in 32 (67%) samples, and for KRAS in 23 (46%) samples. EGFRdelEx19 mutations were detected in four (14%) of the 29 cases that were annotated, and three additional EGFR mutations in 12 (40%) cases. LC-RT-PCR was technically feasible in all cases. All mutations detected by NGS were also detected by LC-RT-PCR. LC-RT-PCR detected three additional KRAS Exon 2 mutations and three additional EGFRdelEx19 mutations. NGS detected additional mutations in 4 cases (2 EGFR Exon 2, 1, KRAS Codon 61, 1 PIK3CA). Conclusion: LC-RT-PCR is a rapid, highly sensitive method to detect mutations of immediate therapeutic relevance, such as EGFRdelEx19 and KRAS Exon 2 mutations, in limited EBUS-TBNA specimens from metastatic NSCLC patients. It is of value as rapid and sensitive initial assay in a two-step diagnostic process for first-line treatment decision, incorporating broader biomarker panels as second step.

Keywords: EGFRdelEx19, KRAS Exon 2, NSCLC, EBUS-TBNA

P3.028-026 ASSOCIATION OF EGFR EXON 19 DELETION AND T790M MUTATION WITH EFFICACY OF EGFR-TKI TREATMENT IN NSCLC PATIENTS

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Background: The most common event responsible for resistance of epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI) is acquisition of the T790M mutation, which occurs in approximately 50% of patients who initially respond to EGFR-TKI. Recently, third-generation EGFR-TKIs have been shown to exert a remarkable effect against T790M resistance mutation-positive non-small cell lung cancer (NSCLC). T790M is an important predictive marker for third-generation EGFR-TKIs; therefore, determining the treatment window for EGFR TKI (EGFR TKI + TKI treatment) is critical. In the present study, we determined the T790M mutation status in plasma and tissue samples harvested from patients treated with EGFR-TKI treatment during the first-line or relapse after EGFR-TKI therapy and correlated the clinical characteristics of the patients with T790M mutation status. Methods: A total of 22 patients were enrolled in this study. Plasma samples were collected before TKI treatment (basal stage) and after TKI treatment (relapse stage). Plasma and tissue samples were analyzed for T790M mutation status using tissue and plasma DNA. Results: The plasma samples of 19 patients (86%) had T790M mutation, whereas the plasma samples of 18 patients (81.8%) had T790M mutation. Tissue samples from 16 patients (72.7%) had T790M mutation. Multivariate analysis revealed that the type of EGFR mutation (exon 19 deletion mutation versus L858R point mutation), p=0.011; OR=2.1, 95% CI=0.05-0.77) and total duration of EGFR-TKI treatment (10 months versus <10 months, p=0.001, OR=9.9, 95% CI=0.02-0.28) were significantly associated with the presence of T790M mutation.

Conclusion: Patients with EGFR exon 19 deletion mutation and long-term treatment with EGFR-TKI exposure demonstrated a high prevalence of T790M mutation. These data are potentially important for clinical decision making in the NSCLC patients with EGFR mutation.

Keywords: non-small cell lung cancer, EGFR, EGFR-TKI, T790M

Poster Session 3: P3.028. Advanced NSCLC & Chemotherapy/Targeted Therapy

Immunotherapy

P3.028-027 DETECTION OF EGFR MUTATIONS IN PLASMA OF LUNG ADENOCARCINOMA PATIENTS USING REAL-TIME PCR AND MASS SPECTROMETRY

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Background: Lung adenocarcinoma patients harbouring sensitizing EGFR mutations can benefit from treatment with tyrosine kinase inhibitors (TKI). Whenever tumour tissue is inadequate or unavailable, detection of EGFR mutations in circulating cell-free tumour (cf) DNA from plasma is crucial to predict and monitor response to therapy. In this study we compared EGFR status between tumour tissue and plasma, using real-time PCR. Moreover, we evaluated the adequacy of ctDNA for a multi-target mass spectrometry (MS) analysis. Methods: EGFR mutations were investigated in paired plasma and tumour tissues from a prospective series of 105 lung adenocarcinoma patients. 79 had no prior TKI treatment and 26 underwent re-biopsy for TKI-acquired resistance. Molecular analyses were performed on tissue by routine MS test (evaluation of 30 hot-spots in 10 genes including EGFR) and on ctDNA by a validated Scorpion/LNA real-time PCR (evaluation of 30 EGFR mutations). In the 26 post-TKI patients ctDNA analysis was performed also by MS. Results: 1 Plasmatic versus tissue by real-time PCR: overall sensitivity, specificity and concordance were 68.4%, 95.4% and 82%. In pre-TKI patients, 17 harboured EGFR sensitizing mutations on tissue, 10 detected also in plasma (sensitivity 58.8%, specificity 100%, concordance 91%). All 26 post-TKI patients preserved EGFR sensitizing mutations. Regarding the detection of EGFR T790M resistance mutation, sensitivity, specificity and concordance were 83.6%, 89% and 73%. Specifically, 11 patients were T790M-positive (62%): 7 on both specimens, 4 only on tissue and 3 only on ctDNA. 2-Plasmatic versus tissue by MS: sensitivity, specificity and concordance for T790M were 50%, 93.3% and 76%. Particularly, 6 patients had a T790M-positive ctDNA: 5 concordant and 1 discordant with tissue; 4 T790M-positive cases on tissue were undetected in plasma, 1 sample was not evaluable. Conclusion: The real-time PCR on ctDNA showed a sensitivity consistent with literature and a high specificity, mostly in pre-TKI group. Concordance rates, influenced by biological and methodological factors, were lower in post-TKI group. Indeed, some T790M mutations were detected only on ctDNA, which is expected to effectively mirror tumour heterogeneity better than biopsic samples, thus giving a global view of tumour. Finally, we demonstrated the adequacy of ctDNA for MS, in terms of quantity and quality. The use of a multi-target analysis on ctdna might improve tumour characterisation and response monitoring, evaluating important oncogenes other than EGFR, like PIK3CA, KRAS and BRAF. However, further studies are needed to better explore MS applicability on ctDNA.

Keywords: Multi-target techniques, lung adenocarcinoma, EGFR mutations, Circulating cell-free DNA

Poster Session 3: P3.028. Advanced NSCLC & Chemotherapy/Targeted Therapy

Immunotherapy

P3.028-028 CHARACTERIZING RESIDUAL ERLOTINIB-TOLERANT POPULATION USING EGFR MUTATED NSCLC PRIMARY DERIVED XENOGRAFTS: THE LAST HOLDOUTS

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Background: Three generations of epidermal growth factor receptor (EGFR)
tyrosine kinase inhibitors (TKIs) have led to multi-fold improvements in progression free survival of advanced stage non-small cell lung cancer (NSCLC) patients carrying EGFR kinase domain mutations. However, cure is not yet achievable for patients with TKI monotherapy. Such patients will eventually progress due to acquired resistance. In vitro evidence suggests that minor populations of epigenetically modified drug tolerant cells (DTCs) may be one important mechanism for tumor cells surviving the TKI. We hypothesize that characterizing the genomic and epigenomic alterations observed in DTCs in vivo and comparing them to the bulk tumour will delineate a number of mechanisms of tolerance exhibited by DTCs. Methods: DTCs were induced via chronic erlotinib treatment of a lung adenocarcinoma primary derived xenograft (PDX) harbouring an erlotinib sensitive exon 19 deletion. Molecular profiles of DTCs are compared to untreated controls via immunohistochemistry (IHC) and gene expression array. We are now undertaking exome-sequencing, assay for transposable-accessible chromatin with high throughput sequencing (ATAC-seq), methylated DNA immunoprecipitation and sequencing (MeDIP-seq). Results: When compared to untreated tumours, DTCs exhibit decreased apoptosis (CC3 IHC) and proliferation (Ki67 IHC). DTCs maintained strong signaling via the EGFR pathway (pERK, pAKT, pS6). DTCs exhibited 2437 significantly differentially expressed genes (DEGs; ±1.5-fold change and adjusted p-value <0.05) including multiple cancer stem cell markers (ALDH1A1, ALDH1A3, CD44). DEGs also were involved in vesicle-mediated transport (including lysosomes, exosomes and endosomes), autophagy, stress/unfolded protein response, cytoskeleton organization, chromatin organization, ion pumps and transporters, cell adhesion, WNT, NOTCH, PI3K and MAPK pathways. DTCs remained resistant to three cycles of cisplatin/veinorlbine either alone or when combined with photodynamic and epigenomic and gene expression results will be presented. Conclusion: DTCs may be a major impediment to cure by single-agent EGFR targeted therapies. Understanding the mechanisms and developing strategies to overcome DTCs may give insights on therapeutic strategy to further improve the survival of EGFR-mutated NSCLC patients.

Keywords: personalized medicine, drug tolerance, persisters, EGFR


P.028-029 PRIMARY DOUBLE EGFR MUTATIONS T790M AND MUTATION IN EXON 19 OR 21 - PREVALENCE AND TREATMENT RESULTS IN SLOVAKIAN NSCLC PATIENTS

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Background: Primary EGFR dual mutations comprising T790M and exon 19 or 21 mutation (SM, sensitizing mutations) are rare when common diagnostic methods are used. There are limited data about the treatment results with EGFR-TKIs in this setting. Purpose of this study was to find out the prevalence of primary dual EGFR mutations T790M and SM in the Caucasian population of NSCLC patients in Slovakia, and to evaluate treatment results with EGFR-TKIs in these patients. Methods: Retrospective multicentre study. The database of the molecular/genetic diagnostic centres were searched for patients with dual EGFR mutations T790M and SM. Data regarding patients were obtained from the databases of participating institutions and patient files. Descriptive statistics was used and a Multiple logistic regression analysis. Results: In total 3883 patients were tested for EGFR mutation from 2010 through 2015. Allele specific PCR was used in majority, high resolution melting analysis, Sanger sequencing and mutant-enriched PCR were also used. Double mutations T790M and SM were found in only six cases, i.e. the observed period prevalence was 0.15%. Patients’ characteristics and the treatment results are in the Table. PS was improved after two months of treatment in patients with initial PS 0 or 1, and remained unchanged in those with PS 1. There were no unexpected AEs.

Table: Characteristics of patients with primary dual EGFR mutations T790M and SM (sensitizing mutation), and results of treatment with EGFR-TKI

<table>
<thead>
<tr>
<th>Gender</th>
<th>Age (years)</th>
<th>Smoking status</th>
<th>PS</th>
<th>Histology</th>
<th>NSCLC Stage</th>
<th>T790M Treatment line (TKI)</th>
<th>Response</th>
<th>PFS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>W 24</td>
<td>Never</td>
<td>AC</td>
<td>IV</td>
<td>NSCLC</td>
<td>T790M</td>
<td>1st/2nd</td>
<td>PR &amp; CR</td>
<td>12</td>
</tr>
<tr>
<td>W 36</td>
<td>Never</td>
<td>AC</td>
<td>IV</td>
<td>NSCLC</td>
<td>T790M</td>
<td>1st/2nd</td>
<td>CR</td>
<td>16</td>
</tr>
<tr>
<td>W 40</td>
<td>Never</td>
<td>AC</td>
<td>IV</td>
<td>NSCLC</td>
<td>T790M</td>
<td>1st/2nd</td>
<td>CR</td>
<td>20</td>
</tr>
<tr>
<td>W 45</td>
<td>Never</td>
<td>AC</td>
<td>IV</td>
<td>NSCLC</td>
<td>T790M</td>
<td>1st/2nd</td>
<td>CR</td>
<td>30</td>
</tr>
<tr>
<td>W 50</td>
<td>Never</td>
<td>AC</td>
<td>IV</td>
<td>NSCLC</td>
<td>T790M</td>
<td>1st/2nd</td>
<td>CR</td>
<td>40</td>
</tr>
<tr>
<td>W 55</td>
<td>Never</td>
<td>AC</td>
<td>IV</td>
<td>NSCLC</td>
<td>T790M</td>
<td>1st/2nd</td>
<td>CR</td>
<td>60</td>
</tr>
<tr>
<td>W 60</td>
<td>Never</td>
<td>AC</td>
<td>IV</td>
<td>NSCLC</td>
<td>T790M</td>
<td>1st/2nd</td>
<td>CR</td>
<td>60</td>
</tr>
<tr>
<td>W 65</td>
<td>Never</td>
<td>AC</td>
<td>IV</td>
<td>NSCLC</td>
<td>T790M</td>
<td>1st/2nd</td>
<td>CR</td>
<td>60</td>
</tr>
</tbody>
</table>

Conclusion: The prevalence of the dual EGFR mutations T790M and SM is very low in Caucasian population in Slovakia when common testing methods are used. Treatment results seen in this study suggest good effectiveness of the first or second generation EGFR-TKIs even in NSCLC with primary dual T790M and SM mutations. The quantitative analysis of these mutations using the blood sample is available at present. It might be useful in decision making about the use of the first – second or the third generation EGFR-TKI, based on the prevailing mutation.

Keywords: T790M, dual mutations, EGFR-TKIs, exon 19 mutation


P.028-030 SINGLE INSTITUTION EXPERIENCE WITH EGFR GENE MUTATION ANALYSIS AND TREATMENT OF EGFR POSITIVE PATIENTS IN THE YEARS 2010 TO 2015

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Background: Our department is among several centers in the Czech Republic which comprehensively diagnose and treat patients with lung cancer, including mutational analysis of EGFR and subsequent personalised treatment. Methods: We present the results of mutational analysis of EGFR gene, and effects of treatment in patients with NSCLC with mutations in this gene who were in treatment in our department in the years 2010 to 2015. We processed the data to get a five year long, single institution experience. Results: In 786 examined patients, 65% were male. Average age was 65.1 years, median 66 years. In these 786 patients, 1039 analyses of EGFR mutation status were done. 10% (79 patients) were EGFR positive. Within the group of EGFR-positive patients 65% were female. Average age was 65.6 years, median age 66 years. 62% (46 patients) with positive EGFR mutation were non-smokers, 33% (25 patients) former smokers and 5% (4 patients) smokers. 92% of patients had adenocarcinomas. The most frequent mutations were in exon 19 and 21. 65% (51 patients) of the EGFR positive group were treated with TKI, in some of the lines of the treatment. TKI was mostly used in the first line of treatment. 35% (28 EGFR positive patients) were not treated with TKI because of PS 3 or 4 (11 patients), prior radical surgery (9 patients) or radical radiotherapy (1 patient). 7 patients left for other center. Median PFS in the group of 23 patients, who were treated with TKI in first line, was 8.0 months (average PFS 8.9 months). The average OS of 31 patients who were treated in the years 2010 to 2015, including lines with chemotherapy, was 18.3 months (median 17, the longest survival 56 and the shortest 2 months). At the beginning of April 2016, 20 patients were still in treatment. The longest survival in this group was 61 months. Three patients with mutation T790M, occurring simultaneously with deletion in exon 19 showed surprisingly good results. One patient was still alive at the beginning of April 2016, and OS of the remaining two patients was 43 and 56 months. Conclusion: The majority of EGFR positive patients were treated with TKI, mostly in the first line. The rest of the patients either did not need TKI therapy, or TKI was not indicated because of their overall poor condition. Our experience is similar to the results of larger multicenter studies.

Keywords: Epidermal growth factor receptor, non-small cell lung cancer, Tyrosin Kinase Inhibitors


P.028-031 T790M: A FAVORABLE MUTATION?

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Background: Patients with lung adenocarcinoma harboring somatic activating mutations in the epidermal growth factor receptor (EGFR) gene have benefited significantly from EGFR tyrosine kinase inhibitors (TKIs). However, a vast majority would eventually develop resistance to such TKIs, resulting in disease progression. T790M, a secondary mutation in exon 20 of the EGFR gene, has been identified as the major mechanism responsible for acquired
EGFR-TKI resistance, accounting for roughly 50% of resistance. However, the association of T790M status and clinical outcome remains elusive. Here, we conducted a retrospective study examining the association between T790M status and prognosis on clinical samples obtained from 43 patients with EGFR-mutant lung adenocarcinoma and later acquired resistance to EGFR-TKIs. Methods: We performed capture-based targeted ultra-deep sequencing on either tumor biopsies or blood samples of 43 lung adenocarcinoma patients, who harbored EGFR mutations, and subsequently developed resistance to EGFR-TKIs. We used BURSTing Rock Biopsy panels, consisting of critical exons and introns, covering multiple classes of somatic mutations, including single nucleotide variation (SNVs), rearrangements, copy number variations (CNVs) and insertions and deletions (INDELS) to detect genetic alterations both qualitatively and quantitatively. Results: We investigated the mutation status after progression of resistance to EGFR-TKIs. Our analysis revealed 64% (18/28) of patients, harboring exon 19 deletions at baseline, acquired T790M at the time of progression. In contrast, only 33% (5/15) of patients, harboring exon 21 L858R substitutions at baseline, acquired T790M, indicating T790M mutation is more commonly found in patients with exon 19 deletions (p=0.052). Next, we associated T790M status with cumulative EGFR-TKI exposure time, and found patients had longer TKI exposure are more likely to acquire T790M mutation. The median TKI exposure time for patients who eventually acquired T790M was 19.20m ± 18.6. In contrast, the median exposure time for patients who never acquired T790M was 12.20m ± 20m (P =0.017). Furthermore, we investigated the presence of T790M mutation with progression free survival (PFS). Our data revealed that 68% (15/22) of patients with PFS >12 months acquired T790M mutation after TKI exposure. In contrast, among patients with PFS <12 months, only 33% of them acquired T790M mutation (p=0.048). Conclusion: Patients who eventually acquired T790M mutation have longer cumulative TKI exposure and are associated with longer PFS before the emergence of drug resistance. In addition, we also discovered that patients harboring exon 19 deletions are more likely to develop T790M mutation. Therefore, T790M status can be used as a potential biomarker for prognosis.

Keywords: rebiopsy, T790M, lung adenocarcinoma, epidermal growth factor receptor (EGFR)

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P3.028-033 FILTER PAPER AS SPECIMEN STORAGE AND TRANSPORT MEDIUM OF EGFR MUTATION TESTING COLLECTED FROM LUNG CANCER PATIENTS IN REMOTE AREAS OF INDONESIA

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Background: Indonesian National Insurance and Formulary mandates EGFR molecular testing for all newly diagnosed lung cancer patients. Cytological smears prepared from pleural effusions are routine sources for molecular testing. However, pathological reviews and molecular diagnostics are not always accessible in many Indonesian remote hospitals. We evaluated filter paper as simple storage and transport medium of pleural effusion sediment to central laboratory. Methods: Pleural effusions obtained from 16 lung cancer patients were split and prepared in two parallel methods, ie smeared on cytological slides and sedimented into filter paper. Cytological slides were reviewed by a pathologist, who selected areas enriched with tumor cells for DNA extraction. Pleural effusion sedimented on filter papers were air dried and DNA were extracted. EGFR mutation was detected using combined PCR High Resolution Melting (HRM) and Restriction Fragment Length Polymorphism (RFLP) having analytical sensitivity of detecting 3% EGFR mutant alleles. EGFR genotypes obtained from cytological slides were compared with those from filter paper to determine specificity and sensitivity. Another set of 63 pleural effusion specimens collected on filter papers were also evaluated and tested for EGFR results. Results: EGFR mutations rates from same patients (N=16) using two different methods were 42.7% and 18.75% using cytology and filter paper, respectively. Mutations L858R (5 cases) and L861Q (1 case) were obtained using cytology, and L858R (3 cases) using filter paper. Agreement between two methods were 75% yielding Kappa value 0.458 (moderate). Diagnostic sensitivity and specificity were 42.86% and 100%, respectively. Another set filter papers with sedimented pleural effusions obtained 63 patients showed 15.9% mutation rate.

Conclusion: Our data demonstrated that filter paper may serve as ancillary medium to store and transport lung specimens for lung patients residing in remote areas and/or where pathology review is not accessible in many parts of this island. In this study, mutation rate (15.9%), sensitivity (62%), specificity (100%) and specificity (100%) using filter paper were similar to mutation rate (22%), sensitivity (47%), specificity (96%) obtained from plasma of Asian lung cancer patients as described recently (Han, B et al 2015). High rate of specificity to detect EGFR mutation may inform therapy choice or diagnosis for patients highly suspected with malignancy. However, poor sensitivity of using filter paper as collection medium points out that patients with negative results should be invited and sent to tertiary hospital for further workup.

Keywords: Lung cancer, pleural effusion, EGFR mutation, Sensitivity and Specificity, Filter paper.

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Table 1 Response

<table>
<thead>
<tr>
<th>Copies/mL</th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10</td>
<td>5</td>
<td>11</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>≥10</td>
<td>8</td>
<td>13</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

Conclusion: Patients benefited from osimertinib treatment independent of T790M copy numbers in the blood samples. Although limited by low numbers, we observed a trend towards better response to osimertinib in patients with ≥10 T790M copies/mL.

Keywords: liquid biopsy, EGFR T790M mutation, osimertinib, advanced NSCLC

**P3.028-035 CELL FREE TUMOR DNA TO MONITOR RESPONSE TO TYROSIINE KINASE INHIBITORS IN PATIENTS WITH EGFR-MUTANT NON-SCAMELL LUNG CANCER**

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Background: Treatment with epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) has improved outcome of EGFR mutant non-small-cell lung cancer (mNSCLC) patients. Monitoring the presence of EGFR sensitizing and resistance (such as T790M) mutations in response to treatment may have a clinical impact on the therapeutic strategy. Detecting these alterations in circulating free tumor DNA (cfDNA) can be an easier and more safe way to obtain information about the EGFR mutational status.

Methods: Analyses have been conducted in NSCLC patients with a tissue-confirmed EGFR mutation treated in first-line setting with TKIs. EGFR-sensitizing and EGFR exon 20 mutations were analyzed in cfDNA extracted from plasma collected at baseline, after 8 and 20 days' treatment, and every 4 months of therapy until progression. EGFR analyses were performed using PANamutyper kit (PANAGENE). Results: Of the 16 mEGFR-NSCLC patients treated with first-line TKIs to date (4 with gefitinib, 2 with erlotinib and 10 with afatinib), 9 (56%) showed EGFR-sensitivity mutation at baseline in cfDNA, 4 had an exon 19 deletion, 1 an exon 21 L861Q mutation and 2 an exon 21 L858R mutation synchronous to exon 20 mutations (one insertion and one T790M point mutation). In these 2 last patients, exon 20 mutations were not identified in tumor tissue. The baseline mutation became undetectable in cfDNA in all the 6 patients with EGFR exon 19 deletion at different time point from the beginning of TKIs: in 5 patients after 21 days and in 1 after 8 days. All these patients had partial response at the first radiological evaluation. The subject harboring EGFR L858R mutation synchronous to exon 20 insertion was responsive to TKI and showed the disappearance of exon 20 insertion in cfDNA at a first clinical evaluation, whereas EGFR L858R disappeared after 4 cycles of treatment. Patient with EGFR L858R and T790M didn’t respond to TKI and progressed after 2 months of treatment. At present 3 out of 9 patients progressed but only one showed appearance of T790M in cfDNA during TKI. In the 7 mEGFR-NSCLC with undetectable cfDNA mutation at baseline no changes were seen during treatment. Conclusion: EGFR mutation analysis in cfDNA could give important information concerning the activity of TKIs. In particular the disappearance of mutation in cfDNA may be an early parameter of response that has to be validated in prospective trials. Moreover, cfDNA may give integrative information with respect to that obtained from tissue analysis, bypassing the problem of tumor heterogeneity.

Keywords: EGFR T790M, free DNA, TKI, Resistance

**P3.028-036 THE PREDICTIVE FACTORS FOR POST-PROGRESSION SURVIVAL AFTER EGFR-TKI FAILURE IN ADVANCED EGFR-MUTANT LUNG CANCER PATIENTS**

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**Pulmonary Medicine, Kameda Medical Center, Kamagawa/Japan**

Background: The treatment strategy of EGFR-mutant non-small-cell lung cancer (NSCLC) with acquired resistance to erlotinib is crucial in lung cancer therapy. Previous studies have reported that T790M mutation is associated with reduced response to TKIs. We performed analysis in patients harboring an EGFR T790M mutation after TKI treatment. The patients were selected according to the presence of T790M. We compared the presence of preexisting T790M clones on the clinical outcome. The aim of our study was to investigate whether pretreatment T790M affect the response to TKIs.

Methods: Patients with advanced NSCLC harboring T790M mutation undergoing tyrosine kinase inhibitor (TKI) therapy were included. EGFR analyses were performed with a methodology as much sensitive as ours by Watanabe et al., 2013. In brief, we showed a pretreatment T790M mutation frequency raising the 80% in a series of lung adenocarcinoma patients harboring an EGFR activating mutation, with no correlation to TKI treatment or resistance. In contrast, we found 28% of cases having T790M before treatment. This discrepancy can be due to the different criteria adopted for samples selection, since our cohort included only patients positive to TKIs. In conclusion, in this preliminary study we did not identify a direct association between the presence of small amounts of pre-TKI T790M mutant alleles and patients’ clinical outcome. However, in order to better assess the impact of T790M in predicting the response to therapy, further studies are needed on larger series of patients are needed.

Keywords: EGFR T790M mutation, TKI therapy, digital PCR, lung adenocarcinoma

**P3.028-037 DOES TISSUE EGFR MUTATION STATUS PREDICT TREATMENT RESPONSE AND MORTALITY IN ADENOCARCINOMA LUNG?**

Anant Mohan 1, Ashutosh Dhanuka 1, Ashraf Ansari 2, Mirza Masroor 3, Kalpana Luthra 4, Alpana Saxena 5, Karan Madan 5, Vijay Hadda 5, G. Khilnani 5, Randep Guleria 5

**Unit of Pathological Anatomy, University Hospital of Pisa, Pisa/Italy; 1 Medical Oncology, Santa Maria Della Misericordia Hospital, Azienda Ospedaliera Di Perugia, Perugia/Italy; 2 Medical Oncology, Istituto Scientifico Romagnolo per Lo Studio e La Cura Dei Tumori (IRST), IRCCS, Meldola/Italy; 3 Medical Oncology, S. Maria Delle Croci Hospital, Rovenna/Italy; 4 Medical Oncology, University Hospital of Pisa, Pisa/Italy; 5 Medical Oncology, University Hospital of Pisa, Pisa/Italy**

Background: The treatment strategy of EGFR-mutant non-small-cell lung cancer (NSCLC) with acquired tolerance for epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) is crucial. In that, we have various treatment options in clinical practice. We think predictive factors affecting for post-progression survival (PPS) after the failure of EGFR-TKIs will provide useful information to clinicians regarding decision of next treatments. However, there were a few studies assessing predictive factors associated with PPS. Methods: We enrolled 85 consecutive advanced or recurrent NSCLC patients with harboring an EGFR mutation treated with EGFR-TKIs (gefitinib, erlotinib or afatinib) and experienced progressive disease (PD) at our institution between February 2004 and May 2016. We evaluated the patient characteristics, progression sites and the treatments following EGFR-TKIs. Progression sites were divided into two groups at each site, the appearance of new lesions (NLs) or the progression of existing lesions (ELS). PPS was calculated from the date of PD after initiation of EGFR-TKIs to the date of patient’s death. Results: Among 85 patients, 78 (91.8%) had major EGFR mutation and 64 (75.3%) had synchronous or asynchronous EGFR activating mutation, with 5.9% (5/85) having T790M before TKI treatment. The progression sites (NLs, ELS) were lung (18.8%, 28.2%), central nervous system (CNS) (15.3%), bone (7.1%, 10.6%) and others (5.9%, 3.5%). Next treatments following EGFR-TKIs failure were continuation of the same EGFR-TKI, 27 (31.8%), switch to another EGFR-TKI, 24 (28.2%), switch to cytotoxic agents, 19 (22.4%), addition of cytotoxic or platinum agents to EGFR-TKI, 8 (9.4%) and best supportive care, 7 (8.2%), respectively. Local therapies such as radiotherapy were included in each treatment. Median PPS was 342 days. The patients over 70 years old were comparable with those in younger patients (median PPS: ≥70 vs. <70 years = 338.7 vs. 333.5 days, p = 0.705). Major EGFR mutation was associated with significantly longer PPS (297.9 vs. 85.7 days, p = 0.021). The patients who exhibited CNS-ELS progression showed the tendency for longer PPS (median PPS: ELS vs. CNS = 619.0 vs. 237.1 vs. 300.2 days, p = 0.080). Conclusion: Major EGFR mutation and the new appearance of CNS lesions may be predictive factors for longer PPS after the failure of EGFR-TKIs.

Keywords: non-small cell lung cancer, Epidermal growth factor receptor tyrosine kinase inhibitor, Reccurrence

**POSTER SESSION 3 – P3.028: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/IMMUNOTHERAPY EGFR BIOMARKERS – WEDNESDAY, DECEMBER 7, 2016**
Background: Targeted therapy with tyrosine kinase inhibitors (TKIs) in EGFR positive patients is associated with superior response rates in Caucasian and East Asian populations. Whether similar response is observed in Asian Indians with lung cancer is not yet clear. We aimed to compare the response rates and survival between EGFR positive and negative patients with advanced adenocarcinoma lung at a tertiary level centre in North India. Methods: Treatment naive patients of adenocarcinoma lung were recruited. All patients underwent complete staging and tissue EGFR mutation analysis using DNA extraction and Polymerase chain reaction. EGFR positive patients were treated with oral Gefitinib 250 mg once daily and EGFR negative patients with 3-weekly cycles of platinum based doublet chemotherapy. Treatment response was evaluated after 3 months of Gefitinib or after 4 cycles of chemotherapy using CT-PET scan and categorized as Complete metabolic remission (CR), partial response (PR), stable disease (SD), and progressive disease (PD). The proportion of responders (CR + PR) and non-responders (SD+PD), and short term survival at 3 months were compared between ERG positive and negative patients. Results: 59 patients completed response evaluation at 3 months / 4 cycles. These included 41 males (59.5%), with a mean (SD) age 55.5 (11.2) years. Majority (89.4%) had metastatic stage IV disease. 34 patients (67.5%) were current or previous smokers, with median smoking index of 400 (range, 0-1500). 76% patients had KPS of 80 or above, and 78% had ECOG of 0-1. Overall, 17 patients (29.3%) were tissue EGFR positive for either of exons 19, 18, or 21. The 3-month outcomes in EGFR positive and negative patients were: complete response – 1.6% vs 0%, partial response – 61% vs 24.4%, stable disease – 5.6% vs 26.8%, progressive disease – 11.1% vs 17.1%, and mortality in 16.7% vs 31.7% respectively. EGFR positive group had higher responders compared to EGFR negative patients (p=0.002) although mortality rate did not differ significantly. Conclusion: EGFR mutation positive patients treated upfront with TKI are more likely to show objective response at 3 months and demonstrate a trend towards longer mortality compared to EGFR negative patients treated with conventional chemotherapy.

Keywords: Adenocarcinoma, EGFR mutation, responder, lung cancer

**P3.02B-038 MOLECULAR DYNAMICS SIMULATION OF EGFR L844V MUTANT SENSITIVE TO AZD9291 IN NON-SMALL CELL LUNG CANCER**

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1Student Research Committee, Kurdistan University of Medical Sciences, Sanandaj/Iran; 2Griffith University & QIMR Berghofer Medical Research Institute, Brisbane/ACT, Australia

Background: The Epidermal growth factor receptor (EGFR) belongs to the ErbB family of Receptors of Tyrosine Kinases (RTK) containing transmembrane domain, an extracellular ligand-binding domain and intracellular region which the tyrosine kinase region which has activity for signal transduction. EGFR has a critical role in the efficient control of cell growth, proliferation, survival and differentiation in cells. Approximately half of cases of triple-negative breast cancer (TNBC) and inflammatory breast cancer (IBC) overexpress EGFR. In many other cancers namely, lung and colon cancer the overexpression of this receptor has been observed as well. In more than 60% of non-small cell lung carcinomas (NSCLCs) mutation in EGFR has been occurred, so EGFR also has become an important therapeutic target for the treatment of these tumors. In recent years, designing drugs to inhibit the activity of this receptor in cancer cells has been on the agenda of Precision Medicine Scientists. Such treatment so called targeted therapy is considered as a new approach to treat cancer, in which the treatment is more effective, specific and has fewer side effects for the patient. These drugs are inhibitors that block extracellular protein or impair a part of Tyrosine kinase activity (TKIs). It is essential to note that mutations in EGFR limit the use of these medicaments. Thus, so far few generations of these drugs have been developed to inhibit the tyrosine kinase activity. The first generations of Tyrosine kinase inhibitors are used in the treatment of patients who have a L858R mutation in EGFR. The second-generation drug could overcome T790M mutation. AZD9291 belongs to third-generation drug and is a potent, selective and irreversible inhibitor of both EGFR sensitive and T790M resistant mutations with less activity towards wild-type EGFR. This drug overcomes the T790M mutation, in addition to the fact that it can overcome sensitive mutants such as L844V. L844V is a mutation in the drug resistant cells and did not lead to constitutive EGFR phosphorylation. Methods: This study examines how AZD9291 drug interact with EGFR protein kinase in LB44V mutant with adopting docking and dynamic molecular simulation using Gromacs software version 4.5.6 to understand how this protein develop sensitive against the mentioned drug. Results: The results of the analysis of RMSD simulation in thirty nanoseconds confirm that the assumptions of the study is correct. Conclusion: AZD9291 as a new inhibitor seems to form a stable interaction with the LB44V mutant.

Keywords: EGFR, LB44V, AZD9291, Molecular dynamics simulation, Docking, NSCLC

**P3.02B-039 ANALYSIS OF PROGNOSTIC FACTOR FOR AFA Tinib TREATED PATIENTS WITH EGFR MUTATION POSITIVE NSCLC**

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Background: Aftinib, known as irreversible EGFR-TKI, significantly improved PFS and OS versus cisplatin-based chemotherapy, in combined analysis of LUX-Lung 3 and 6 despite this it was not proved in treatment with former reversible agents. We have tried to examine the factors correlated to improvement of survival in patients treated with afitinib compared to gefitinib or erlotinib. Methods: Patients who were enrolled in clinical trials from 2008 to 2014, and treated with EGFR-TKI as first line treatment were eligible. To explain the difference of tumor response of “re-challenge” EGFR-TKI, and duration of subsequent EGFR-TKI after first line EGFR-TKI failed as “re-challenge”, 7 patients were treated with reversible TKIs, 8 with gefitinib, 4 with erlotinib. Seven patients were treated with afitinib. Median PFS for reversible TKI group versus afitinib group was 397 vs 422 days (P = 0.810). Median OS for reversible TKI group versus afitinib group was 741 vs 1380 days (P = 0.501). There was no difference between the two groups, ageP(0.347), sexP(0.217), stageP(0.891), and mutation typeP(0.581). Eleven patients received subsequent EGFR-TKI after first line EGFR-TKI failed as “re-challenge”, 7 patients in reversible TKI group, and 4 patients in afitinib group. There is no difference of tumor response of “re-challenge” EGFR-TKI, and duration of treatment with EGFR-TKI, in two groups. Conclusion: The patient treated with afitinib tends to live longer in terms of overall survival. But there were no significant correlated factor between clinical characteristics and duration of survival.

Keywords: EGFR-TKI, prognostic factor

**P3.02B-040 A COMPARISON OF DDPCR AND ARMS FOR DETECTING EGFR T790M STATUS FROM ADVANCED NSCLC PATIENTS WITH ACQUIRED EGFR-TKI RESISTANCE**

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Background: To assess the ability of droplet digital PCR and ARMS technology to detect epidermal growth factor receptor (EGFR) T790M mutations from circulating tumor DNA (ctDNA) in advanced non-small cell lung cancer (NSCLC) patients with acquired EGFR-TKI resistance. A sensitive and convenient method for detecting T790M mutation would be desirable to direct patient sequential treatment strategy. To assess the ability of droplet digital PCR and ARMS technology to detect epidermal growth factor receptor (EGFR) T790M mutations from circulating tumor DNA (ctDNA) in advanced non-small cell lung cancer (NSCLC) patients with acquired EGFR-TKI resistance. A sensitive and convenient method for detecting T790M mutation would be desirable to direct patient sequential treatment strategy. Methods: A comparison of two platforms for detecting EGFR mutations in plasma ctDNA was undertaken. Plasma samples and tumor samples were collected from...
patients happening acquired EGFR-TKI resistance in the JHCC study hospital from December 2014 to December 2015. Extracted ctDNA was analyzed using two platforms (Dropseq Digital PCR and ARMS (dPCR)). The ratios between the patients before and after TKI treatment were 0.05. The T790M ctDNA status detected in plasma were analyzed. Results: A total of 108 patients were enrolled in this study. 108 patient plasma samples were detected by ddPCR and 75 were detected by ARMS. All 16 patients experienced an objective response. The median duration of response was 12.3 months (95% CI: 6.7 — 22.7 months). The frequency of objective response was 34% (95% CI: 24% — 45%). Conclusion: Our study demonstrates that ddPCR provide feasibility and sensitivity in analyzing EGFR T790M status in plasma samples from NSCLC patients with acquired EGFR-TKI resistance. The 790M-positive patients have better clinical outcomes to EGFR-TKIs than patients with T790M negative.

Keywords: EGFR, ddPCR, T790M, non-small cell lung cancer.
Background: Molecular testing of the EGFR gene is required to predict therapeutic response in non-small cell lung cancer (NSCLC). Although routinely performed, analysis of tumor tissue is subject to limitations. Analysis of circulating tumor DNA (ctDNA) in blood plasma may overcome these barriers, with techniques to detect and quantify variants in ctDNA are emerging. However, several key elements like sensitivity and specificity still need to be addressed. This study evaluates the inter-laboratory performance and reproducibility of the cobas® EGFR Mutation Test v2 for the detection of common EGFR variants in plasma. Methods: Fourteen laboratories from ten European countries received two identical panels of 27 single-blinded plasma members (Roche Molecular Systems, CA, USA). Samples were wild-type or spiked with plasma DNA containing seven common EGFR variants at six predefined concentrations from 50-5000 target copies per ml (cp/ml). ctDNA was extracted by the Roche cobas® ctDNA Sample Preparation kit. Each sample was analyzed by duplicate analysis with the Roche cobas® EGFR Mutation Test v2 kit. All sites received hands-on training and two obligatory proficiency samples to assure operator qualification. Statistical analyses were performed with SAS 9.4 (SAS Institute Inc., NC, USA). Results: In total, 0.8% (12/1512) and 0.2% (3/1726) of runs were excluded due to protocol deviations or technical failures respectively. The sensitivity was lowest for the c.2156G>G (G719A) variant with values of 80.4%, 69.6% and 83.1% at 50, 100 and 250 cp/ml respectively. Besides 88.7% for the c.2537T>G (L858R) variant at 50 cp/ml, sensitivities for all other variants or concentrations varied between 93.6-100.0% and improved at increasing cp/ml. Specificities were all >88.8%-100.0%. Coefficients of variation (CV) indicate good intra-laboratory repeatability and inter-laboratory reproducibility, but increased for decreasing concentrations. Highest CV’s were reported for: c.2156G>G (G719A), c.2307<2308Ins (G719S), and c.2537T>G (L858R) at 50 cp/ml. Prediction models reveal a significant correlation between the observed semi-quantitative index values (SQI) and copy numbers in plasma for all variants. A systematic over- and underestimation was observed for four different variants at 1000 and 5000 cp/ml respectively. Conclusion: This study demonstrates an overall robust performance of the cobas® EGFR Mutation Test v2 plasma, suggesting a valuable and convenient additional to molecular tumor analysis in NSCLC. Repeated tests are advisable in case of low SQI values to reduce the average variation. Prediction models could be applied by future users to estimate the plasma tumor load from the observed SQI value, taking into account the possibility of systematic errors for high target copies.

Keywords: liquid biopsy, ctDNA, EGFR mutation analysis, plasma

P3.028-044 AFTINIB VERSUS GEFITINIB AS FIRST-LINE TREATMENT FOR EGFR MUTATION-POSITIVE NSCLC PATIENTS AGED ≥75 YEARS: SUBGROUP ANALYSIS OF LUX-LUNG 7
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Background: The irreversible ErbB family blocker afatinib and the reversible EGFR tyrosine kinase inhibitor gefitinib are approved for first-line treatment of patients with activating EGFR mutations. A phase 2 study in elderly NSCLC patients with EGFR mutations (LUX-Lung 7) showed a superior progression-free survival (PFS) for afatinib compared to gefitinib (HR 0.73, 95% CI: 0.57-0.95, p=0.017). The incidence of treatment-related adverse events (TEAEs) for both drugs was comparable. Here we evaluated the efficacy and safety of afatinib and gefitinib in patients aged ≥75 years in two subgroups of the LUX-Lung 7 study (NCT01666660). Methods: Treatment-naive patients with stage IIB/IV EGFRm+ NSCLC were randomized (1:1) to oral afatinib (40 mg/day) or gefitinib (250 mg/day), stratified by EGFR mutation type (Del19/L858R) and presence of brain metastases (Yes/No). Co-primary end points were PFS, TTF, and overall survival. Subgroup analyses of PFS and adverse events (AEs) by age (≥75 years) were exploratory. Results: Of 319 patients randomized in LIT, 40 (13%) were aged ≥75 years (afatinib n=19, gefitinib n=22). Median PFS for both age groups was in line with the overall population and favoured afatinib versus gefitinib (patients ≥75 years: 14.7 vs 10.8 months, HR=0.69 [95% CI: 0.33-1.44], p<0.001; patients <75 years: 11.0 vs 10.9 months, HR=0.76 [95% CI: 0.58-1.00]). The incidence of treatment-related AEs (grade 3/4) was slightly higher in the older subgroup (afatinib: 42%/0%; gefitinib: 24%/5%) than in the younger subgroup (afatinib: 28%/2%; gefitinib: 15%/4%). There were no unexpected safety findings. The most common treatment-related AEs (all grade (3) with in the older patient subgroup were diarrhea (89% [21%], rash [63% (5%)], dry skin [37% (0%)], and decreased appetite (32% [0%]). Dose reduction/discontinuation of afatinib due to treatment-related AEs was required in 53%/16% and 40%/5% of the older and younger subgroup, respectively. Conclusion: A small subgroup of patients in the LUX-Lung 7 trial were ≥75 years old (13%). In exploratory subgroup analyses patients aged ≥75 and <75 years old, advancing age did not adversely affect the PFS benefit and tolerability observed with afatinib versus gefitinib in treatment-naive EGFRm+ NSCLC patients. These findings suggest that afatinib can provide an effective and tolerable treatment for older patients with EGFRm+ NSCLC.

Keywords: NSCLC, elderly, afatinib, gefitinib

P3.028-045 PATRITUMAB PLUS ERLOTINIB IN EGFR WILD-TYPE ADVANCED NON–SMALL CELL LUNG CANCER (NSCLC): PART A RESULTS OF HER3-LUNG STUDY
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Background: Patritumab is a fully human monoclonal antibody that inhibits human epidermal growth factor receptor 3. In a subgroup analysis of the phase 2 HERALD study, addition of patritumab to erlotinib increased progression-free survival (PFS) in advanced NSCLC patients with high tumor expression of heregulin mRNA (HRG-High); a similar safety profile was seen with patritumab-erlotinib versus erlotinib. This 2-part, phase 3 study (HER3-Lung) investigated erlotinib plus patritumab in advanced, EGFR wild-type NSCLC patients previously treated with a platinum doublet. The primary objective of Part A was to confirm PFS improvement in HRG-High subjects. Methods: HER3-Lung was a 2-part, randomized, placebo-controlled, double-blind study. Subjects aged ≥20 years with known HRG expression, advanced NSCLC previously treated with 1–2 prior systemic therapies including a platinum doublet, and EGFR wild-type (if adenocarcinoma histology) were eligible. Subjects were stratified by HRG expression, histology subtype (adenocarcinoma, squamous-cell carcinoma/NOS), ECOG performance status (0–1), and best response to most recent therapy (CR/PR/SD, PD). Within each stratum, subjects were randomized 1:1 to erlotinib-patritumab or erlotinib-placebo. Results: One-hundred forty-five subjects were randomized, and 125 had discontinued study prior to the data cutoff date. Most common reason for discontinuation was progressive disease (n=70). In the erlotinib-patritumab and erlotinib-placebo arms, respectively, treatment-emergent adverse events (TEAEs) grade ≥3 were reported in 40.5% and 46.5% and any grade serious TEAEs in 35.4% and 36.6% of subjects. Most common TEAEs (by subject) in the erlotinib-patritumab and erlotinib-placebo arms, respectively, were diarrhea (51.4%, 31%) and rash (37.8%, 36.6%). Patritumab did not increase erlotinib efficacy in the intent-to-treat group or HRG subgroups (Table). The study was stopped at the end of Part A because efficacy criteria to proceed into Part B were not reached. Conclusion: HER3-Lung did not confirm patritumab efficacy in the HRG-High subgroup. Safety of patritumab in combination with erlotinib was acceptable.

(See Table next page)
Abstracts

**P3.028-046** AFATINIB BENEFITS PATIENTS WITH CONFIRMED/ SUSPECTED EGFR MUTANT NSCLC, UNSUITABLE FOR CHEMOTHERAPY (SIMPLE PHASE II TRIAL).

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Background: Afatinib is licensed for EGFR mutant NSCLC without prior TKI therapy, but its efficacy and toxicity in patients unsuitable for platinum-doublet chemotherapy is unknown. One previous study suggested that TKIs could benefit medically unfit EGFR-mutant East Asian patients. We conducted the first such study in a Western population. Methods: Single arm phase II trial. Eligible patients with histologically confirmed NSCLC, comorbidities precluding chemotherapy, with either: (i) confirmed EGFR-mutation (no suspected EGFR-mutation) or (ii) suspected EGFR-mutation (no suitable target for genotyping or failed genotyping), but never/former-light smoker, adenocarcinoma and PS 0-2. Patients received oral afatinib (20-40mg daily) until disease progression/toxicity. CT scans performed 4 weeks after starting treatment then every 8 weeks in first year until progression, thereafter every 12 weeks. Primary endpoint was 6-month RECIST-defined progression-free-survival (target 30%). Results: 39 patients were recruited across 14 UK centres (March 2013-August 2015). Median age 72 years (range 36-90); 30 females, 9 males; 20 confirmed and 19 suspected EGFR-mutation; 8 former and 11 never smokers (among suspected EGFR positives), 1,730 in each stage IA,IIA,IIIB,IV; and 27 PS 0-1, 12 PS 2-3. As of July 2016, 7 patients were still taking afatinib (median time on drug 11 months, range 10-16), and 11 stopped for toxicity. 23/39 patients had at least one grade ≥ 3 afatinib-related toxicity (all grade 3, except two with grade 4 [sepsis and hypokalemia]), one fatal pneumonitis), mainly: n=13 diarrhoea; n=4 vomiting; n=3 dehydration; n=3 mouth ulcer, all expected for afatinib, and unsurprising in this unfit group. The table shows efficacy. 6-month PFS rate (58%) far exceeded the 30% target; similarly for patients with confirmed (74%) or suspected (41%) EGFR-mutation.

<table>
<thead>
<tr>
<th>Efficacy endpoint</th>
<th>PFS confirmed</th>
<th>PFS suspected</th>
<th>Median, months (95%CI)</th>
<th>Overall PFS (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy endpoint</td>
<td>7.9 (6.7-10.2)</td>
<td>15.5 (10.9-25.1)</td>
<td>15.2 (10.9-25.1)</td>
<td>15.5 (10.9-25.1)</td>
</tr>
</tbody>
</table>

Conclusion: The toxicity rate was higher compared to that in fitter patients, but afatinib seems to improve PFS and OS in unfit EGFR-mutant NSCLC, and in suspected-positive patients who would otherwise only receive best supportive care.

Keywords: NSCLC, afatinib, mutation, EGFR
EGFR tyrosine kinase inhibitors (TKIs) induce early activation of several signaling pathways. Interleukin-6 (IL-6) and signal transducer and activator of transcription 3 (STAT3) hyper-activation occur following EGFR TKI therapy in EGFR-mutant NSCLC cells. We explored the relevance of co-targeting EGFR, STAT3 and Src-YES-associated protein 1 (YAP1) signaling in EGFR-mutant NSCLC. Methods: We combined in vitro and in vivo approaches to explore whether co-concomitant activation of STAT3 and Src-YAP1 could limit the effectiveness of EGFR TKIs in EGFR-mutant NSCLC cells and xenograft models. In two cohorts of EGFR-mutant NSCLC patients, we examined messenger RNA (mRNA) gene expression within signaling pathways, leading to EGFR TKI resistance. Results: Gefitinib suppressed EGFR, ERK1/2 and AKT phosphorylation but increased STAT3 phosphorylation (pSTAT3-Tyr705). In EGFR mutant cells, gefitinib plus TP-CA1 (STAT3 inhibitor) abolished pSTAT3-Tyr705 but not the YAP1 phosphorylation on tyrosine 357 by Src family kinases (SKFs). The triple combination of gefitinib, TP-CA1 and AZD0530 (SKF inhibitor) abolished both STAT3 and YAP1 phosphorylation and was highly synergistic, according to the combination index. In two EGFR mutant xenograft mouse models, the triple combination of gefitinib, TP-CA1 and AZD0530 markedly and safely suppressed tumor growth. High levels of STAT3 or YAP1 mRNA expression were associated with worse outcome to EGFR TKI in 64 EGFR-mutant NSCLC patients. Median progression-free survival (PFS) was 9.6 (95% CI, 5.9-14.4) and 18.4 months (95% CI, 8.8-30.2) for patients with high and low STAT3 mRNA, respectively (p=0.001), (HR for disease progression, 3.02; 95% CI, 1.5-6.9; p=0.0013). Median PFS was 9.6 (95% CI, 7.7-15.2) and 23.4 months (95% CI, 13.0-28.1) for patients with high and low YAP1 mRNA expression respectively (p=0.005), (HR for disease progression, 2.57; 95% CI, 1.3-5.09; p=0.0067). The results were similar in the validation cohort of 55 EGFR-mutant NSCLC patients treated with first-line EGFR TKI in the Department of Oncology of Shanghai Pulmonary Hospital. Conclusion: Our study reveals that STAT3 and Src-YAP1 signaling activation occurs following single EGFR TKI in EGFR-mutant NSCLC. STAT3 and YAP1 mRNA levels were significantly predictive of progression-free survival in the original as well as in the validation cohort of EGFR-mutant NSCLC patients. Co-targeting STAT3 and Src in combination with EGFR TKI could substantially improve survival.

Keywords: lung cancer, STAT3 signaling, EGFR Inhibitor, YAP1 signaling.

P3.028-049 ORAL VINORELBINE MONOTHERAPY IN PATIENTS WITH EGFR+ NSCLC AFTER FAILURE OF EGFR-TKI IN FIRST LINE: A PROSPECTIVE STUDY

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Background: In advanced metastatic EGFR+ NSCLC patients (pts) progressing after EGFR-TKIs failure in first line, single-agent chemotherapy (CT) may be offered in pts who are unfit for a platinum combination. In this study (NAVOTRIAL 2), oral vinorelbine (NVBo) was evaluated as monotherapy in advanced NSCLC EGFR+ pts who failed to EGFR-TKI in first line. Methods: Phase II, prospective, multicentre, open-label, international study. Main eligibility criteria: stage IIIB/IV NSCLC, EGFR+, prior EGFR-TKI treatment failure, Karnofsky PS ≥70, no prior CT or immunotherapy. Study treatment until progression or unacceptable toxicity: NVBo 60 mg/m² weekly for 3 weeks (first cycle), followed by 80 mg/m² weekly for subsequent cycles in absence of grade 3/4 toxicity. The primary endpoint was the disease control rate (DCR = CR + PR + SD, RECIST 1.1). Results: Final results: 30 pts included (March 2013 - November 2014). Main pts characteristics: median age 66.8 years (60–66 years), median Karnofsky PS 90%, Adenocarcinoma 96.2%, ≥3 organs involved (53.3%). All pts harboured EGFR mutation and received prior EGFR-TKI therapy. Gefitinib 73.3%, Erlotinib 16.7%, Afinatin 10%; 33.3% of pts had ≥2 comorbidities; Total number of cycles: 166 (443 doses administered); median number of cycles: 3.5 (range 1-20); median relative dose intensity: 77.6% (range 46.8-105); dose escalation performed in 76.7% of pts; Disease control rate 63.3% (95% CI [43.8-80]) and 23.3% of patients with stable disease ≥6 months. Median time to treatment failure: 2.7 months (range 0.4-13.6). Median PFS of 3.9 months (95% CI [1.6-5.4]) and OS of 13.1 months (95% CI [6.1-15.8]). Grade 3/4 toxicities per pt: neutropenia 53.3%, anemia 6.7%, leukopenia 26.7%, fatigue 16.7%, nausea 3.3% and vomiting 6.7%. Three cases of febrile neutropenia reported. No grade 3/4 diarrhea, constipation, peripheral neuropathies or alopecia. Conclusion: NVBo as single-agent CT is a well-tolerated option in advanced EGFR-NSCLC pts beyond failure of EGFR-TKI in first line. Its favourable tolerability profile allows a prolonged disease control in non-progressing pts.

Keywords: NSCLC, Oral Vinorelbine, EGFR-positive tumours.
(EGFR-TKI) drastically prolonged progression free survival (PFS) of patients with non-squamous non-small-cell lung cancer (NSCLC) harboring EGFR mutations. However, most cases show tumor regrowth after approximately only 10 months treatment, and the prognosis is still poor. Then it is necessary to make new strategy of treatment for NSCLC harboring EGFR mutation, and we designed phase I/II study of Erlotinib, Carboplatin, Pemetrexed and Bevacizumab in chemotherapy-naive patients with EGFR mutation positive advanced non-squamous NSCLC. Methods: In the phase I part, eligible patients were administrated orally Erlotinib daily, and Pemetrexed, Carboplatin and Bevacizumab intravenously every three weeks for four cycles with maintenance of Pemetrexed and Bevacizumab until PD. The dose level of Erlotinib were 100mg in level 1 and 150mg in level 2. And the dose of pemetrexed, carboplatin and bevacizumab were fixed as 500mg per m², AUC6 and 15mg per kg. The dose limiting toxicities are Grade (Gr) 3-4. DLT events were observed in Phase I. Table1

Fever was observed in level 1, and a Gr3 of neutropenia without fever, three was one and female were five. Histology of all patients was adenocarcinoma, and Evaluation of adverse events. Results: Six patients were enrolled in Phase I part (level 1-three, level 2-three). The median age was 71.5 y.o. (Range, 46-76 y.o). Male was one and female were five. Histology of all patients was adenocarcinoma, and Ex19del was four and Ex21L858R was two. A Gr3 of neutropenia without fever was observed in level 1, and a Gr3 of neutropenia without fever, three Gr3 thrombocytopenia and a stomatitis were observed in level 2(Table1). No DLT events were observed in Phase I. Table1

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<tr>
<th>Grade</th>
<th>1</th>
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<tbody>
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<td>ANC</td>
<td>1</td>
<td>1</td>
<td>1</td>
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<tr>
<td>PLT</td>
<td>2</td>
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<tr>
<td>Anemia</td>
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<td>Transaminase</td>
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<td>T.Bil</td>
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<td>Fatigue</td>
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<td>Diarrhea</td>
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</table>

Conclusion: The recommend dose of Erlotinib is 150mg daily.

Keywords: EGFR, Erlotinib, bevacizumab, pemetrexed

Whereas the 7T90M mutation confers prolonged survival and sensitivity to 3rd generation TKIs, there is no data on outcome and treatment of MET-driven resistant EGFR-mutated NSCLC patients. Methods: Molecular and clinicopathological data from patients with advanced EGFR-mutated NSCLC and MET overexpression or amplification on a post-progression (PP) sample obtained after treatment with EGFR TKI were retrospectively reviewed in 15 nationwide centers. MET overexpression was defined by MET immunohistochemistry (IHC) score 3+ and MET amplification was assessed by FISH analysis and defined by MET/CEP7 ratio >2 or MET copy number >8. Results: 43 patients were included (26 del19, 16 L858R and 3 rare EGFR mutations). The median time between EGFR TKI initiation and PP biopsy was 13.8 months [2.1-61.3]. On PP biopsy, 20 tumors tested for FISH (53%) had MET amplification and all out of 37 samples tested for IHC were scored 3+. No epithelial to mesenchymal transformation was observed. A 7T90M mutation was found in 12/42 (29%) PP biopsies. 5 patients had both MET amplification and 7T90M mutation. The median overall survival (OS), and the median PP OS were 36.2 months [IC95%: 27.3-45.6] and 18.5 months [IC95%: 10.6-26.5], respectively. 16 patients received 7T90M mutation in 1 out of 2 patients treated with a combination of MET and EGFR TKIs. No significant difference was found according to the MET FISH status for OS and PP OS.

Keywords: MET, amplification, non-small cell lung cancer, EGFR mutation, TKI resistance
Results: 96 patients were randomized and 91 patients were treated at 14 centers in Korea. The characteristics of pemetrexed plus cisplatin (PC) arm (N=48) and pemetrexed alone (P) arm (N=48) were well balanced; the median age was 60 vs 64 years old, 37 vs 33 patients were females; 39 vs 43 patients were ECOG PS 1. The ORR of PC arm (N=46) was 34.8% (16/46), while P arm (N=45) was 17.8% (8/45). With 20.4 (range 4.1-33.4) months of follow-up, the median PFS was 5.4 months (95% confidence interval [CI], 4.5-6.3) in PC arm and 6.4 months (95% CI, 3.6-9.2) in P arm (p = .313). One-year survival rate was 77% for PC arm, 68% for P arm, respectively. The most common adverse events include anorexia (N=34, 37.4%), nausea (N=24, 26.4%), neuropathy (N=10, 11.0%) and skin change (N=10, 11.0%). Adverse events ≥ Grade 3 were in 12 patients (26.1%) in PC arm and 8 patients (17.8%) in P arm. Dose reduction (5-21%) in 5 patients (10.9%) and dose delay (7-42%) in 6 patients (12.3%) were more frequent in PC arm. With 385 pairs of questionnaire of EORTC QLQ-C30 and QLQ-LC13 obtained from 94 patients, overall, the time trends of HRQOL were not significantly different between two arms. Further analysis of survival data will be updated. Conclusion: Pemetrexed plus cisplatin combination therapy showed higher adverse rate than pemetrexed monotherapy without significant difference in PFS. There was no significant difference in quality of life between two arms.

Keywords: Cisplatin, non-small cell lung cancer, EGFR mutation, pemetrexed

P3.02B-054 EGFR MUTATION PROFILE IN NEWLY DIAGNOSED LUNG ADENOCARCINOMA IN PERSAHABATAN HOSPITAL, JAKARTA-INDONESIA
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Background: In Indonesia, gefitinib or erlotinib were given for free under National Health System Insurance, for EGFR sensitizing mutation positive patients. Our previous study showed proportion of common EGFR mutation in Indonesian patients, however, the proportion of uncommon mutation and resistant mutation were not yet known. Here we report the spectrum of EGFR mutation among newly diagnosed therapy naïve adenocarcinoma NSCLC in respiratory referral hospital, Persahabatan Hospital, Jakarta Indonesia. Methods: Newly diagnosed-therapy naïve lung adenocarcinoma were evaluated for EGFR mutation between September 2015-April 2016. Four exons of EGFR were tested using a combination of PCR High Resolution Melting, fragment sizing, and direct DNA sequencing. Results: One hundred and thirty nine subjects were enrolled from September 2015 to March 2016 in Persahabatan hospital, with distribution 63% were male, and 56 years old (mean). Most specimens were obtained using bronchoscopy (31%) followed by TTNA (30%) and pleural effusion (17%). Overall EGFR mutation rate was 61.9%, and more frequent in female (72% of female subjects has EGFR mutation whereas only 55% of male subjects has positive results). Of the positive EGFR mutation subjects; 1% has exon 18 G719S; 5.8% exon 18 G719S; 17.5% Exon 19 In/Del; 43% Exon 21 L858R; and 21% Exon 21 L861Q. The incidence of primary resistant Exon 20 T790M mutation was 11.6% and more frequent in female. Conclusion: EGFR mutation is common in Indonesian population of newly diagnosed naïve adenocarcinoma NSCLC. Baseline rate of T790M was not rare when detected using standard direct DNA sequencing. Further study is needed to elaborate proportion of primary resistant and biological mechanism in Indonesian lung cancer patients.

Keywords: primary resistant, NSCLC, Adenocarcinoma, EGFR mutation

Poster Session 3 - P3.02B: Advanced NSCLC & Chemotherapy/Targeted Therapy/Immunotherapy - EGFR Clinical - Wednesday, December 7, 2016

P3.02B-055 IMPACT OF Pemetrexed CHEMOTHERAPY IN EXON 19 AND 21 MUTATED NSCLC
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Background: EGFR mutation subtype is being increasingly recognized as factor impacting outcome of patients receiving oral TKI in non-small cell lung cancer. Data for the effect of this factor on the outcome in patients receiving...
Keywords: EGFR mutation, pemetrexed, exon 19, exon 21

**P3.028-056 SURVIVAL IN EGFR MUTATED ADVANCED LUNG CANCER ADENOCARCINOMA PATIENTS - A NATIONAL STUDY**

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**Background:** The Danish Lung Cancer Registry (DLCR) has since 2003 reported all cases of lung cancer in Denmark. Since 2012 data on EGFR mutations and ALK translocations have also been included in the registry. The significance of being EGFR mutated on survival in a national population has not yet been reported. Methods: All Danish lung cancer patients are ascertained based on coded information in the National Patient Register and the National Pathology Registry (NPR). Based on SNOMED coding the subgroups of lung cancer and the EGFR mutation status is identified. The study includes all Danish stage IIIB and IV lung cancer adenocarcinoma patients diagnosed between 2013 and 2015. Treatment modalities including EGFR inhibitors followed international guidelines. Survival of the EGFR mutated patients has been compared to EGFR negative patients and those without any EGFR registration. Prognostic factors were analyzed in a Cox uni- and multivariate analysis. Results: Among 3120 patients identified, 244 were EGFR positive, 1921 were treated until progression or unacceptable toxicity (post 6 cycles, patients were offered maintenance pemetrexed every 21 days). Results: 143 patients received pemetrexed based therapy as first line treatment for stage III/IV NSCLC in the chemotherapy arm. 51 patients (38%) had exon 21 mutation while 92 patients (64%) had exon 19 mutation. Response rates in evaluable patients was 47.7% in exon 19 patients (41 patients, n=86) and 42.9% in exon 21 patients (18 patients, n=42). There was a differential impact of EGFR mutation on OS (p=0.028, HR:1.787, 95% CI 1.066-2.998) in favour of exon 19 mutation. They also had a significant increase in median overall survival (24.5 months, 95% CI 21.3-27.7 months) over the exon 21 mutated patients (18.1 months, 95% CI 13.6-22.6 months, p=0.002). Conclusion: In this study, EGFR exon 19 mutation had a differential impact on both OS and OS in Indian patients of advanced-stage NSCLC treated with chemotherapy.

**Keywords:** EGFR mutation, pemetrexed, exon 19, exon 21

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**P3.028-057 NETWORK META-ANALYSIS OF FIRST-LINE AND MAINTENANCE REGIMENS IN EGFR MUTATED ADVANCED NON-SMALL-CELL LUNG CANCER (NSCLC)**

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**Background:** More evidence is needed to select the best first line treatment strategy for patients harboring EGFR mutations and its subtypes. Methods: We performed a systematic search and included studies reporting OS and/or PFS efficacy estimates by EGFR mutation status or subtypes (Del19/ L858R). Hazard ratios of competing treatments were pooled using a Bayesian hierarchical model incorporating both within and between study heterogeneities. Treatment benefits were evaluated using posterior hazard ratios with 95% credible intervals (CrI) and ranked by surface under the cumulative ranking curve (SUCRA) for OS benefit. Results: 4,177 records were screened and 20 trials were meta-analyzed. Statistically significant OS and PFS benefits were seen with (i) first-line intercalated chemotherapy+erlotinib in EGFR mutation positive and (ii) first-line afatinib in Del19. In L858R, OS benefit was seen only with (i) first-line intercalated chemotherapy+erlotinib and (ii) first-line afatinib in Del19. In L858R, no OS benefit was seen although treatments showed PFS benefits.

**First-line Maintenance**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>OS</th>
<th>PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erlotinib</td>
<td>0.48 (0.26-0.88)</td>
<td>0.25 (0.15-0.43)</td>
</tr>
<tr>
<td>Erlotinib + bevacizumab</td>
<td>0.40 (0.11-1.52)</td>
<td>0.18 (0.09-0.36)</td>
</tr>
<tr>
<td>Afatinib</td>
<td>0.90 (0.74-1.10)</td>
<td>0.38 (0.20-0.70)</td>
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<tr>
<td>Bevacizumab</td>
<td>0.30 (0.36-0.20)</td>
<td>0.23 (0.13-0.40)</td>
</tr>
<tr>
<td>Erlotinib + bevacizumab</td>
<td>0.54 (0.18-0.32)</td>
<td>0.23 (0.10-0.80)</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>1.00 (0.66-1.50)</td>
<td>0.49 (0.18-1.31)</td>
</tr>
<tr>
<td>Gefitinib</td>
<td>1.03 (0.83-1.30)</td>
<td>0.32 (0.24-0.42)</td>
</tr>
<tr>
<td>Gefitinib</td>
<td>1.03 (0.86-1.23)</td>
<td>0.45 (0.37-0.56)</td>
</tr>
</tbody>
</table>

**Keywords:** non small cell lung cancer, meta-analysis, EGFR

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Median survival for EGFR positives was 544 days, against 203 for EGFR negatives and 114 for untested. The EGFR mutated group had more female patients, never smokers and lower Charlson Comorbidity Index (CCI) than the 2 other groups. Supplementary data on population characteristics and treatment are to be presented. In univariate Cox analysis EGFR was an independent predictor for survival (HR: 0.68 (95% CI: 0.82-0.74); P=0.000) and in the multivariate analysis adjusted for age, sex, smoking and CCI the effect of EGFR was independent (HR: 0.72 (95% CI: 0.69 – 0.80); P=0.000).

**Conclusion:** Among all available strategies, first-line intercalated chemotherapy+erlotinib in EGFR mutation positive and afatinib in Del19 are the only strategies showing both OS and PFS benefits.

**Keywords:** non small cell lung cancer, meta-analysis, EGFR

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**P3.028-057 NETWORK META-ANALYSIS OF FIRST-LINE AND MAINTENANCE REGIMENS IN EGFR MUTATED ADVANCED NON-SMALL-CELL LUNG CANCER (NSCLC)**

Gilberto De Lima Lopes
Grupo Oncoclinicas, São Paulo/Brazil
P3.028-058 SECOND-LINE THERAPY IN EGFR ACTIVATING MUTATION POSITIVE ADVANCED NSCLC: ANALYSIS FROM A RANDOMIZED PHASE III FIRST-LINE TRIAL

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Background: To evaluate the efficacy of second line therapy in patients progressing on either a Pemetrexed-Platinum doublet or Gefitinib in an experimental growth factor receptor (EGFR) activating mutation positive Stage IIIb/IV non small cohort in the setting of a phase III clinical trial evaluating Pemetrexed-Platinum doublet versus Gefitinib as first line therapy. Methods: Patients were part of a randomized Phase III open label parallel group study comparing Gefitinib with Pemetrexed-Platinum doublet in the upfront setting in an EGFR mutation positive Stage IIIb/IV lung cancer population. On progression on first-line therapy, patients were started on second line therapy, if Eastern Cooperative Oncology Group (ECOG) performance status (PS) was 0-2 and baseline clinical and biochemical parameters were within acceptable limits. Patients who received Pemetrexed-Platinum in the first line were offered Gefitinib in the second line while patients progressing on first-line Gefitinib were considered for Pemetrexed-Platinum doublet as second-line therapy. Results: 187 patients were included for analysis. Out of these 157 patients were evaluable for response. 113 patients had received gefitinib as second line, while 74 patients had received other I. V second line chemotherapies. The median OS rate was 60.6 % in Gefitinib cohort (60, n=98), and 33% in non-Gefitinib cohort (18, n=58), p=0.30. The median PFS was 7.4 months (95% CI: 4.5-9.4) in gefitinib cohort, whereas it was 4.4 months in non-Gefitinib cohort (95% CI: 3.7-5.2). Median OS in gefitinib cohort was 14 months (95% CI: 10.8-17.2), while it was 9.8 months in non-gefitinib cohort (95% CI: 7.8-11.7)p=0.007 Conclusion: Patients started on gefitinib post progression on pemetrexed therapy had significant benefit, whereas it was limited in patients who received I.V chemotherapy post Gefitinib.

Keywords: NSCLC, survival, Second Line, EGFR mutation positive

Poster Session 3 - P3.028: Advanced NSCLC & Chemotherapy/Targeted Therapy/Immunotherapy
EGFR Clinical – Wednesday, December 7, 2016

P3.028-060 COMPARATIVE ANALYSIS OF THE EFFICACY OF THREE 1ST/2ND GENERATION EGFR-TKIS FOR EGFR MUTATED NSCLC IN CLINICAL PRACTICE

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Background: EGFR-TKIs show promising anti-tumor activities for EGFR mutated NSCLC, and three EGFR-TKIs, gefitinib (GEF), erlotinib (ERL) and afatinib (AFA), are available for treatment of NSCLC harboring an EGFR mutation in first-line settings in Japan. Which EGFR-TKI is optimal for first-line therapy in clinical practice, however, is not yet known. Methods: We reviewed all patients who were diagnosed with EGFR mutated NSCLC between January 2010 and April 2016 at two institutions in Mutsu, Japan. The aim of this retrospective study was to evaluate three EGFR-TKIs using time to treatment failure (TTF), overall survival (OS) and the response rate (RR) in clinical practice. TTF analysis was conducted on all patients, while OS analysis was conducted on patients in stages 3B or 4. Either chi-square statistics or a Fisher’s exact test was used where appropriate to compare proportions among groups. Survival curves were calculated using the Kaplan-Meier method, and were compared using the log-rank test. Results: A total of 310 patients were diagnosed with EGFR mutated NSCLC in the three institutions. Of the 310 patients, 145 patients treated with EGFR-TKIs were enrolled. The median age was 70 years old (range 37-95), 88 patients (62.9%) were female and 97 patients were never-smokers. Almost all patients (96.3%) were diagnosed with adenocarcinoma, with 52.4% diagnosed with ExI19 deletion, and 44.8% diagnosed with Ex21L858R. 82 patients received gefitinib as the first EGFR-TKI, while 35 patients received erlotinib, and the remaining 28 patients received afatinib. The efficacy assessment demonstrated that there was no significant difference in TTF (4.9m;GEF, 5.3m;ERL, 5.2m;AFA), OS (12m;GEF, 14m;ERL, 16m;AFA), and the presence of a major mutation were predictive factors for a longer TTF of EGFR-TKI therapy. OS of patients with brain metastasis (BM) was significantly shorter than those without BM. (p=0.018) Conclusion: This study demonstrated a tendency of afatinib to be superior, however, there was no significant difference in TTF and OS among the three EGFR-TKIs as the results of submission. These results indicated that all EGFR-TKIs had equal clinical benefit at presence, with a potential superiority for afatinib. Further prospective investigations are warranted to evaluate the efficacy of these three EGFR-TKIs in clinical practice to confirm these results.

Keywords: EGFR mutated NSCLC, EGFR-TKI

Poster Session 3 – P3.028: Advanced NSCLC & Chemotherapy/Targeted Therapy/Immunotherapy
EGFR Clinical – Wednesday, December 7, 2016

P3.028-061 A PHASE II STUDY OF NAB-PACLITAXEL (NAB-P) IN PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC) WITH EGFR MUTATIONS

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Background: Bone metastasis is frequent in non-small cell lung cancer (NSCLC) patients, and subsequent skeletal related events (SREs) adversely deteriorate life quality and survival. Patients harboring sensitive epidermal growth factor receptor (EGFR) activating mutation experience a prolonged life expectancy. However, it is unclear whether survival enhancement in NSCLC patients with sensitive EGFR mutation may encounter an increase in the onset of SREs or not. Also, it is still unknown whether time to SREs is impacted by EGFR mutation status. In this study, we evaluated the impact of EGFR mutation status and other clinic-pathological variables on the incidence of SREs and on survival outcomes of SREs in stage IV NSCLC patients. Methods: We conducted a retrospective study of medical records from patients who were diagnosed stage IV NSCLC in a single institute. EGFR mutation status, and other clinical-pathological variables, bone metastasis outcomes and survival data were collected and statistically analyzed. Results: 410 patients with evident bone metastasis and positive EGFR mutation in the study. 43.0% of patients were detected with sensitive EGFR mutation, and 29.0% were prophylactically administered bisphosphonate. 42.7% experienced at least one SRE, the most common type of which was palliative radiotherapy. Patient harboring sensitive EGFR mutation hold a lower incidence of SREs than patients who were detected with wild type EGFR (37.3% vs 47.8%, p=0.031), and patients who received bisphosphonate confronted a lower incidence of SRE comparing with patients who didn’t receive bisphosphonate prophylactically (36.1% vs 45.4%, p=0.087). Median time from bone metastasis to first SRE was two months longer in patients with EGFR mutation, comparing to patients with wild type EGFR, with a marginal significance (5.0m vs 3.0m, p=0.08). The administration of bisphosphonate delayed the median time to first SRE for 5 months (7.0m vs 2.0m, p=0.037). In multivariate analysis using a Cox proportion model, wild type EGFR (HR=1.555, 95%CI:1.081-2.248), multiple bone lesions (HR=1.991, 95%CI: 1.217-3.258), mixed type bone lesions (HR=2.344, 95%CI:1.085-4.238) were independent risk factors of survival post first SRE, while a smoking history (HR=1.428, p=0.053) was shown marginaly significant with an impaired survival post first SRE. Conclusion: This retrospective study shows that EGFR mutation has a propensity to impact the onset of SRE and prolong survival post first SRE in patients with stage IV NSCLC. For patients with higher risks to experience SREs, bisphosphonate is an alternative to impede the process.

Keywords: non-small cell lung cancer, bone metastasis, skeletal related events, Epidemical growth factor receptor
Background: Patients with NSCLC harboring a sensitizing EGFR mutation have effective targeted therapy options initially but most patients eventually need to receive cytotoxic chemotherapy. We previously reported our institutional experience with taxane based therapy in this patient population and this provided the rationale for the currently ongoing phase II study (NCT01620190). Methods: Patients with EGFR mutation positive NSCLC who were refractory to tyrosine kinase inhibitor (TKI) therapy and chemotherapy naive received nab-P at 125mg/m² on days 1, 8, and 15 in a 28-day cycle. The primary endpoint was response rate which was assessed using RECIST v1.1. Results: As of data cut-off of March 14, 2016, 22 patients were enrolled and received therapy (19 evaluable, 2 not evaluable, 1 patient excluded due to not being eligible). Median age was 65 (range 56-77), 75% of patients were women, 40% did not have a smoking history and majority (65%) of patients had an ECOG performance status of 1. Tumor histology consisted mostly of adenocarcinoma (90%); 55% of patients harbored exon 21 L858R and 45% harbored exon deletion 19 mutations. Confirmed partial response was documented in 8 of 19 (42%) patients with a median duration of response of 4.3 months (range 3.3-9.5) and stable disease was documented in 4 of 19 (21%) patients with a disease control rate of 63%. Median progression free survival was 4.4 months (95% CI 1.8-5.5 months). The most common grade 3 treatment-related adverse events (AE) were peripheral neuropathy (10%), fatigue (10%) and neutropenia (15%). There were no treatment-related grade 4 AEs. Conclusion: Single agent nab-P has promising activity in patients with EGFR mutation positive NSCLC. The AE profile was consistent with previously reported AEs in the literature. Accrual of patients continues and updated data will be presented.

Keywords: nab-paclitaxel, EGFR, chemo

Poster Session 3 – P.028: Advanced NSCLC & Chemotherapy/Targeted Therapy/Immunotherapy
EGFR Clinical – Wednesday, December 7, 2016

P.028-062 SAFETY OF NECITUMUMAB AND ABEMACICLIB COMBINATION THERAPY IN PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC)

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Background: Trials of anti-EGFR necitumumab and the CDK4 and CDK6 inhibitor abemaciclib have demonstrated anti-tumor activity of each agent in patients with NSCLC in a xenograft model of NSCLC, the addition of necitumumab to abemaciclib improved the anti-tumor efficacy compared to either monotherapy. Methods: Single-arm, multicenter Phase Ib study to investigate the combination of necitumumab and abemaciclib in patients with stage IV NSCLC (NCT02411591). The safety interim population includes squamous and non-squamous patients treated with the recommended dose of necitumumab 800mg IV on days 1 and 8, every 21 days in combination with abemaciclib 150mg (dose identified in preceding dose escalation part of study) administered every 12 hours on days 1–21. Major eligibility criteria include: progression after platinum-based chemotherapy regimen and maximum 1 other prior chemotherapy for advanced and/or metastatic disease (prior treatment with EGFR-TKI and ALK inhibitors was mandatory in patients whose tumor has EGFR-activating mutations or ALK translocations, respectively); ECOG PS 0-1; tumor tissue availability for biomarker analysis and measurable disease. Treatment will continue until disease progression, unacceptable toxicity, or withdrawal of consent by the patient, or sponsor/investigator decision. Results: This safety interim includes 16 squamous and non-squamous patients treated at recommended dose (necitumumab 800mg + abemaciclib 150mg) and having completed 2 cycles of study treatment (or otherwise discontinued study treatment). The most common (≥15%) patients adverse events (AEs) of any grade are shown in the Table. Grade ≥3 AEs were reported in 6 patients (diarrhea, nausea, vomiting, neutropenia, decreased appetite, hypophosphatemia, dyspnoea were each reported in 1 patient and fatigue in 2 patients); grade ≥3 AEs were judged to be related to study treatment in 4 patients. No patients have discontinued the study due an AE.

Keywords: abemaciclib, non-small cell lung cancer, Necitumumab

Poster Session 3 – P.028: Advanced NSCLC & Chemotherapy/Targeted Therapy/Immunotherapy
EGFR Clinical – Wednesday, December 7, 2016

P.028-063 ANALYSIS OF SURVIVAL IN EGFR-MUTATION-POSITIVE ADVANCED NON-SMALL-CELL LUNG CANCER PATIENTS WITH MILIARY PULMONARY METASTASIS

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Background: Backgrounds: Miliary pulmonary metastasis is more frequent in patients harboring EGFR mutations, and dramatic responses are often observed after treatment with EGFR-tyrosine kinase inhibitors (TKI). The relevance between miliary pulmonary metastasis and EGFR mutation has often observed after treatment with EGFR-tyrosine kinase inhibitors (TKI). The relevance between miliary pulmonary metastasis and EGFR mutation has been suggested; therefore, we analyzed the survival in patients with miliary pulmonary metastasis harboring EGFR mutations treated with EGFR-TKI. Methods: Methods: We retrospectively analyzed 269 patients diagnosed with advanced or recurrent NSCLC treated with EGFR-TKI between 2005 and 2015 identified from the electronic database at our hospital. OS and PFS were estimated using the Kaplan–Meier method. We analyzed the survival in all eligible patients and performed propensity score matching based on clinical characteristics. Results: Results: A total of 215 NSCLC patients harboring EGFR mutations and treated with EGFR-TKIs were included in the study. Patients had a median age of 61 years (38–88 years). With regard to EGFR-TKIs, gefitinib was administered in 167 patients (77.%)
BACKGROUND: This study was designed to evaluate the response and outcomes from March 2006 to December 2015 were retrospectively included. Patients with advanced stage NSCLC positive for EGFR activating mutation treated in our Comprehensive cancer center (Centre Francois Baclesse, Caen, France) from March 2006 to December 2015 were prospectively included. Patients may have been directly referred by their general practitioner or by pulmonary physicians who had usually performed the diagnostic biopsy. In such a situation, the histological analysis was performed outside of our hospital. Molecular analysis was performed in both cases in our hospital. Demographic data were collected, the place where the histological analysis was performed, the time to treatment was identical vs 36 days when it was performed outside. Conclusion: A high proportion of patients received EGFR-TKI as first line treatment (80%) and 17 (20%) did not. Reasons will be presented at meeting. The proportion of patients who had received both TKI and intravenous chemotherapy (mainly Paclitaxel and platinum, 80 patients) were selected for this analysis. The treatment regimens, response in accordance with RECIST v1.1 and treatment outcomes were noted. Descriptive statistics was performed. Kaplan Meier survival analysis was used for estimation of PFS and OS. Results: 85 patients received third line therapy of which weekly paclitaxel was given in 43 (50.6%) patients, Docetaxel in 15 (17.6%) patients, Gemcitabine in 6 (7.1%) patients, and Toremifene in 11 (13%) patients and other chemotherapy in 10 (11.8%) patients. Out of 85 patients, 67 were evaluable for response; 13 (19.4%) patients had partial response, 34 (50.7%) patients had stable disease and 20 (29.9%) patients had progression as best response. In 7 patients chemotherapy had to be stopped because of toxicity in 5 patients and patients preference in 2 patients. The median PFS & OS were 4.2 months (95% CI 3.4-4.9 months) and 8.4 months (95% CI 6.9-9.9 months) respectively. There was no difference in PFS and OS between weekly Paclitaxel and other regimens. Conclusion: Third line therapy in EGFR mutated patients post TKI and Paclitaxel progression is associated with meaningful PFS and OS.

Keywords: EGFR, mutation-positive, advanced non-small-cell lung cancer, molecular pulmonary metastasis

P3.028-066 PHASE II TRIAL OF THE C-MET INHIBITOR TEPOTINIB IN ADVANCED LUNG ADENOCARCINOMA WITH MET EXON 14 SKIPPING MUTATIONS AFTER FAILURE OF PRIOR THERAPY
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Background: The MET proto-oncogene is activated in 3-4% of lung adenocarcinomas through mutations that lead to aberrant mRNA splicing and skipping of exon 14, which encodes a region of the c-Met protein that regulates its degradation. c-Met lacking exon 14 accumulates as a functional receptor on the cell surface and appears to act as a true oncoprotein, active in several phase I/II trials, with activity appearing greatest in c-Met-positive tumors. The recommended dose has been established as 500 mg/ day. This open-label phase II trial (EUDRACT 2015-005563-31) is investigating the efficacy of tepotinib in patients with lung adenocarcinoma harboring MET mutations that cause exon 14 skipping. Methods: Eligible patients are adults with historically confirmed stage IIIb/IV lung adenocarcinoma who have failed at least one line of systemic therapy, including a platinum doublet-containing regimen, and have failed no more than two active therapies. Tumors cannot harbor EGFR mutations that confer sensitivity to EGFR TKIs, or ALK rearrangements, but must exhibit MET mutations that are known to lead to exon 14 skipping, confirmed by a central laboratory. The primary objective is to assess the efficacy of tepotinib according to confirmed objective response as per independent review determined by RECIST v1.1.

Secondary objectives include further assessment of efficacy, and assessment of safety, pharmacokinetics, and quality of life. Patients receive tepotinib 500 mg/day in 21 day cycles until disease progression, intolerable toxicity, or withdrawal from treatment for other reasons. Recruitment of 60 patients in Europe, USA, and Japan is planned. This trial will establish the activity, safety, and tolerability of tepotinib in patients with lung adenocarcinoma harboring c-Met exon 14 alterations. Results: section not applicable Conclusion: section not applicable

Keywords: c-Met, lung adenocarcinoma, tepotinib, exon 14

P3.028-067 A SINGLE-INSTITUTION EXPERIENCE OF AFATINIB IN PATIENTS WITH EGFR-MUTATED ADVANCED NON-SMALL CELL LUNG CANCER
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Background: This study was designed to evaluate the response and outcomes to third line chemotherapy in classic activating EGFR mutation positive non small cell lung cancer (NSCLC) who had progressed on both TKI and intravenous chemotherapy Methods: 85 EGFR mutation positive NSCLC patients who had received both TKI and intravenous chemotherapy (mainly Paclitaxel and platinum, 80 patients) were selected for this analysis. The treatment regimens, response in accordance with RECIST v1.1 and treatment outcomes were noted. Descriptive statistics was performed. Kaplan Meier survival analysis was used for estimation of PFS and OS. Results: 85 patients received third line therapy of which weekly paclitaxel was given in 43 (50.6%) patients, Docetaxel in 15 (17.6%) patients, Gemcitabine in 6 (7.1%) patients, and Toremifene in 11 (13%) patients and other chemotherapy in 10 (11.8%) patients. Out of 85 patients, 67 were evaluable for response; 13 (19.4%) patients had partial response, 34 (50.7%) patients had stable disease and 20 (29.9%) patients had progression as best response. In 7 patients chemotherapy had to be stopped because of toxicity in 5 patients and patients preference in 2 patients. The median PFS & OS were 4.2 months (95% CI 3.4-4.9 months) and 8.4 months (95% CI 6.9-9.9 months) respectively. There was no difference in PFS and OS between weekly Paclitaxel and other regimens. Conclusion: Third line therapy in EGFR mutated patients post TKI and Paclitaxel progression is associated with meaningful PFS and OS.

Keywords: NSCLC, Third line chemotherapy, EGFR, positive, advanced

P3.028-064 TIME TO EGFR-TKI TREATMENT FOR PATIENTS WITH ADVANCED NSCLC AND EGFR ACTIVATING MUTATION IN A TERTIARY CANCER CENTER
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Background: IPASS was the first study to demonstrate that EGFR-TKI was a valuable option as first line treatment for patients with advanced NSCLC and EGFR activating mutations (Mok TS et al, N Engl J Med 2009, 361:947-57). To apply this strategy, it is essential that the results of the molecular analysis are quickly available. The objective of our study is first to determine which proportion of patients started EGFR-TKI as first line treatment during the last ten years in our institute, and secondly to calculate the time interval from the initial biopsy to the start of EGFR-TKI treatment. Methods: All patients with advanced stage NSCLC positive for EGFR activating mutation treated in our Comprehensive cancer center (Centre Francois Baclesse, Caen, France) from March 2006 to December 2015 were retrospectively included. Patients may have been directly referred by their general practitioner or by pulmonary physicians who had usually performed the diagnostic biopsy. In such a situation, the histological analysis was performed outside of our hospital. Molecular analysis was performed in both cases in our hospital. Demographic data were collected, the place where the histological analysis was performed, and time from biopsy to the start of first systemic treatment (EGFR-TKI or chemotherapy). Results: Eighty-six patients were included. Sixty-nine (80%) patients received EGFR-TKI as first line treatment (80%) and 17 (20%) did not. Reasons will be presented at meeting. The median time from initial biopsy to EGFR-TKI treatment was 26 days. The median time from initial biopsy to EGFR-TKI treatment was different according to the place where patients had their biopsy performed. 18 days when the biopsy was performed in our center vs 36 days when it was performed outside. Conclusion: A high proportion of patients could start EGFR-TKI as first line treatment (80%). Median time to treatment was longer in our center than what has been reported in a recent study. Most patients could start EGFR-TKI as first line treatment (80%). Median time to treatment was 36 days when it was performed outside. Conclusion: A high proportion of patients received EGFR-TKI as first line treatment (80%) and 17 (20%) did not.

Keywords: EGFR mutation

P3.028-065 THIRD LINE THERAPY IN EGFR POSITIVE ADVANCED NON-SMALL CELL LUNG CANCER
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Background: This study was designed to evaluate the response and outcomes to third line chemotherapy in classic activating EGFR mutation positive
Background: Aftinib, an irreversible ErbB family blocker, inhibits EGFR, HER2, and HER4. LUX-Lung 1 and 4 showed that aftinib was effective for patients with EGFR-mutated non-small cell lung cancer (NSCLC) who experienced progression after chemotherapy and gefitinib/erlotinib therapy. LUX-Lung 3 and 6 showed that aftinib had a significantly better response rate and prolonged progression free survival (PFS) compared with pemetrexed plus cisplatin or gemcitabine plus cisplatin in a first-line setting. However, these trials recruited only patients who met inclusion criteria. Thus, the relevance of the outcomes needs to be examined in a clinical setting. Moreover, diarrhea and skin rash are frequently observed in patients receiving aftinib. Establishing optimal management of adverse events is essential to improve clinical outcomes and quality of life in patients receiving aftinib. Methods: We retrospectively reviewed chart records of 15 EGFR-mutated NSCLC patients who had received aftinib from July 2014 to August 2015 at our institution. Results: Median age was 68 years (range, 53–72 years). Fourteen patients had adenocarcinoma. Nine and 4 patients had Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 and 1, respectively. Three and 6 patients were treated as first- and third-line therapies, respectively. Thirteen patients had exon 19 deletion. One patient harbored both an L858R mutation in exon 21 and a de novo T790M mutation in exon 20. PFS of the 3 patients who were treated with aftinib as first-line therapy was 0.9, 6.8, and 16.4 months. Median PFS of 12 patients who had previous EGFR-TKI therapy was 4.0 months (95% confidential interval 2.1–5.9 months). The de novo T790M NSCLC patient experienced disease progression at 1.3 months. The response rate of pretreated patients was 16%. Fourteen patients were treated with aftinib 40 mg/day. One patient began aftinib 20 mg/day because of ECOG PS 2. Dose reduction was required in 8 (53%) patients. Grade 3 or 4 adverse events occurred in 3 (20%) patients. One patient had grade 3 paronychia and another patient had grade 3 diarrhea. Both patients could continue aftinib with dose reduction. Five patients had reduction of aftinib to 30 mg/day and 2 patients required reduction by 10–mg decrements down to 20 mg/day. Conclusion: Clinical outcomes in terms of PFS and objective response rate of aftinib in our EGFR-mutated NSCLC patients with prior therapy were comparable to LUX-Lung 1 and 4. Adverse events were tolerable and manageable with careful dose reduction.

Keywords: aftinib, Non-small-cell lung cancer, EGFR mutation

Conclusion: Gefitinib was well tolerated; however RR and PFS were lower than those reported in clinical trials, possibly reflecting our small, unselected population. High ACE 27 score, PS2 and LB58R mutation were significantly associated with inferior survival.

P3.028-069 TO ASSESS EFFICACY OF FIRST LINE TKIS IN EGFR MUTANT ADVANCED NSCLC PATIENTS FROM NORTH INDIA
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Medical Oncology, Rajiv Gandhi Cancer Institute and Research Centre, Delhi/India Background: The reversible EGFR tyrosine kinase inhibitors gefitinib and erlotinib are approved for first-line treatment of EGFR mutation-positive non-small-cell lung cancer (NSCLC). However, here is paucity of data on their efficacy from the Indian subcontinent Methods: This is a retrospective analysis including 43 patients. These patients were treated at a tertiary care center in north India. Advanced NSCLC patients (stage IV) having sensitive EGFR mutation who were treated with gefitinib (250 mg per day) or erlotinib (150 mg per day) were analysed for their outcome. Subgroup analysis by EGFR mutation (19,20,(21), sex and status according to brain metastasis was also done using SPSS. Results: 43 patients with stage IV non-squamous NSCLC with EGFR sensitive mutation were treated with first line TKI. There were 16 male and 27 female patients with mean age of 62.5 years (ranging from 43 to 85 years). Mean PFS for all the patients on first line TKI was 11.63 months Mean PFS for male patients was 9.93 months and for female patients it was 12.7 months . There were 26 patients with exon 19 deletions and 16 with exon 21 mutation and 1 with exon 18 mutation. Mean PFS in patients with exon 19 deletions was 11.11 months and 10.44 months in patients with exon 21 mutation. Mean PFS in patients on erlotinib was 12.7 months (CI 6.2-18.3) and 11.4 months in patients on gefitinib. Twelve patients (27.9%) out of 43 had brain metastases. PFS of these 12 patients was 10.33 months and 12.08 months for patients without brain metastases. Conclusion. Erlotinib and gefitinib significantly improves PFS of 12 patients with sensitive EGFR mutations. PFS is better in female patients, exon 19 mutation/deletion and without brain metastases in North Indian population. Keywords: NSCLC, EGFR mutation, TKIs, PFS

P3.028-070 NSCLC WITH DETECTABLE EGFR MUTATION: INSTITUTIONAL EXPERIENCE
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1 Oncology, Hospital Italiano, Buenos Aires/Argentina, 2 Pathology, Hospital Italiano, Buenos Aires/Argentina Background: EGFR is one of the most commonly mutated proto-oncogenes in lung cancer. The frequency of such mutations varies from approximately 10% of lung adenocarcinomas in North American and European populations to as high as 50% in Asia. The leucine to arginine substitution at position 858 (L858R) in exon 21 and short in-frame deletions in exon 19 are the most common sensitizing mutations, comprising approximately 90% of cases. Approximately 50% of EGFR TKI resistance is due to a second site mutation, the T790M mutation occurring within exon 20. We describe our experience in patients with lung cancer with detectable EGFR mutation. Methods: Describe
Background: Bone involvement has been considered as an adverse predictive factor in the systemic treatment of majority of malignant tumors. New horizon, opened with targeted agents, especially in lung cancer, faced us with encouraging results of treatment in advanced cancer patient population. Gefitinib, for the first time in tyrosine kinase inhibitor (TKI), has been a standard first-line treatment for EGFR mutated lung adenocarcinoma patients in Serbia since 2011. Methods: Fifty-one consecutive patients (pts) with advanced lung adenocarcinoma and EGFR mutation were treated with 1st line gefitinib at IORS since 2011. Fourteen of them were with bone metastases (BM). We compared treatment outcome of BM group (n=14) with group of pts without BM (n=20).

Results: We found 61 /326 (18.7%) patients with detectable EGFR mutation, 27 patients (177%) with detectable EGFR mutation, 27 patients had advanced or unrescetable disease. The most common sites of metastases were bone and lymph nodes. 27 of the 61 patients had mutation of exon 19, 27 patients with mutation of exon 21, others in 18 and 20. Five of them with detectable T790M mutation confirmed by repeat biopsy after progressing to ITK. The most common side effects were diarrhea and rash, 12 patients had toxicities which had to reduce dose or discontinue treatment. Conclusion: The most common side effects were diarrhea and rash, 12 patients had toxicities which had to reduce dose or discontinue treatment. We had a low incidence of invalid or not evaluable biopsies. Although all patients with detectable mutation were treated with ITK, who received such treatment had good adhesion and a low percentage of patients had to discontinue treatment.

Keywords: EGFR, lung cancer, NSCLC

POSTER SESSION 3 – P3.02B: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/ IMMUNOTHERAPY
EGFR CLINICAL - WEDNESDAY, DECEMBER 7, 2016

P3.028-071 FIRST-LINE GEFITINIB FOR EGFR-MUTATED LUNG ADENOCARCINOMA PATIENTS WITH BONE METASTASES - A SINGLE INSTITUTION EXPERIENCE
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Background: The role of EGFR tyrosine kinase inhibitors in the second-line for patients with squamous non-small-cell lung cancer (NSCLC) remains unclear. We conducted a prospective phase II study to assess use of gefitinib in patients with squamous NSCLC as second-line chemotherapy, and investigated the predictive and prognostic value of a proteomic signature using VeriStrat test. Methods: Between December 2011 and October 2015, 56 patients with histologically confirmed, second-line, Stage IIIIB or IV NSCLC were enrolled in 9 centres in Republic of Korea. Patients were treated with gefitinib (250 mg per day orally). The proteomic test classification was masked for patients and investigators. The primary end point was disease control rate (DCR) at 8-weeks, and the secondary end points included toxicity, progression-free survival (PFS), overall survival (OS), and correlation between the serum proteomic test classification and treatment. This study is registered with ClinicalTrials.gov, number NCT01485809. Results: The median age was 69 years (range, 41-83) and 55 (98%) patients were male, and 49 (88%) had an ECOG PS of 1. Fifty five (98%) of patients had received platinum-based chemotherapy. The DCR at 8 weeks was 50.0% (95% confidence interval [CI] 34.8-63.4). With a median follow-up of 5.5 months, the median PFS and OS were 2.8 (95% CI 1.3-4.3) and 6.4 (5.4-7.4) months, respectively. Of the most common adverse event was rash (16 [29%]) and diarrhea (14 [25%]). Pretreatment plasma was available for 50 samples, and VeriStrat testing was successful in 45 samples (90%) with 71% classified as Good. The median PFS of VeriStrat Good was 3.2 (95% CI 1.9-4.7) and 2.4 (1.5-3.3) months for VeriStrat Good vs. Poor patients, respectively (p=0.069). The median OS of VeriStrat Good was longer than those of VeriStrat Poor (11.4 [5.7-17.0] vs 4.8 [2.5-7.0] months), which was not statistically significant (p=0.052). Conclusion: These data suggest that gefitinib is modest activity as second-line chemotherapy in patients with squamous NSCLC. Serum proteomic test using VeriStrat is not prognostic for both OS and PFS among squamous NSCLC patients treated with gefitinib.

Keywords: Prospective study, NSCLC, gefitinib

POSTER SESSION 3 – P3.028: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/ IMMUNOTHERAPY
EGFR CLINICAL - WEDNESDAY, DECEMBER 7, 2016

P3.028-073 A PHASE II, LIQUID BIOPSY STUDY USING DIGITAL PCR IN EGFR MUTATED, LUNG CANCER PATIENTS TREATED WITH AFNATIBIN (WJ08 B114LTR)
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Background: There is a need for an effective strategy to select patients who are more likely to benefit from treatment with EGFR tyrosine kinase inhibitors (TKIs). Liquid biopsy of plasma DNA is a minimally invasive method to detect circulating tumor DNA (ctDNA) of EGFR mutations. The aims of the study were to investigate the diagnostic accuracy of liquid biopsy in EGFR mutated NSCLC, most of whom were single-institutional, retrospective studies. Methods: West Japan Oncology Group (WJOG) B114LTR is a multi-institutional, prospective liquid biopsy study in advanced NSCLC. Chemotherapy naive, advanced NSCLC patients with EGFR-sensitizing mutation will receive afatinib monotherapy (40 mg/body) until progressive disease (PD) or unacceptable toxicity. Plasma DNA will be obtained from patients at baseline, 2, 4, 8, 12, 24, 48, and at 52 weeks. At three times of common EGFR mutations (exon 19 deletion, exon 20 T790M and exon 21 L858R) will be analyzed using plasma DNA with multiplexed, pico-droplet digital PCR assay (RainDrop® system, RainDance Technologies, Billerica, MA).

Keywords: Prospective study, NSCLC, gefitinib

POSTER SESSION 3 – P3.028: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/ IMMUNOTHERAPY
EGFR CLINICAL - WEDNESDAY, DECEMBER 7, 2016

P3.028-072 A MULTICENTER PHASE II STUDY OF GEFITINIB IN SQUAMOUS NSCLC PATIENTS WHO FAILED FIRST-LINE CHEMOTHERAPY
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Background: The background of the EGFR tyrosine kinase inhibitors in the second-line for patients with squamous non-small-cell lung cancer (NSCLC) remains unclear. We conducted a prospective phase II study to assess use of gefitinib in patients with squamous NSCLC as second-line chemotherapy, and investigated the predictive and prognostic value of a proteomic signature using VeriStrat test. Results: Between December 2011 and October 2015, 56 patients with histologically confirmed, second-line, Stage IIIIB or IV NSCLC were enrolled in 9 centres in Republic of Korea. Patients were treated with gefitinib (250 mg per day orally). The proteomic test classification was masked for patients and investigators. The primary end point was disease control rate (DCR) at 8-weeks, and the secondary end points included toxicity, progression-free survival (PFS), overall survival (OS), and correlation between the serum proteomic test classification and treatment. This study is registered with ClinicalTrials.gov, number NCT01485809. Results: The median age was 69 years (range, 41-83) and 55 (98%) patients were male, and 49 (88%) had an ECOG PS of 1. Fifty five (98%) of patients had received platinum-based chemotherapy. The DCR at 8 weeks was 50.0% (95% confidence interval [CI] 34.8-63.4). With a median follow-up of 5.5 months, the median PFS and OS were 2.8 (95% CI 1.3-4.3) and 6.4 (5.4-7.4) months, respectively. Of the most common adverse event was rash (16 [29%]) and diarrhea (14 [25%]). Pretreatment plasma was available for 50 samples, and VeriStrat testing was successful in 45 samples (90%) with 71% classified as Good. The median PFS of VeriStrat Good was 3.2 (95% CI 1.9-4.7) and 2.4 (1.5-3.3) months for VeriStrat Good vs. Poor patients, respectively (p=0.069). The median OS of VeriStrat Good was longer than those of VeriStrat Poor (11.4 [5.7-17.0] vs 4.8 [2.5-7.0] months), which was not statistically significant (p=0.052). Conclusion: These data suggest that gefitinib is modest activity as second-line chemotherapy in patients with squamous NSCLC. Serum proteomic test using VeriStrat is not prognostic for both OS and PFS among squamous NSCLC patients treated with gefitinib.

Keywords: Prospective study, NSCLC, gefitinib
Primary endpoint of this study is the concordance of EGFR mutation status between tissue and plasma at baseline. Secondary endpoints are overall response rate, progression-free survival and safety. This is the first report on the primary endpoint and early remission rate based on mutated cf-DNA. This study was registered at UMIN (ID: 000015847). Results: Fifty-seven patients were registered and samples from 55 patients were analyzed. Clinical characteristics were as follows; median age: 69 years, male / female: 25/30, PS 0/1: 23/32, c-stage III / IV: post-operative relapse: 2/37/16, exon 19 deletion / exon 21 L858R: 28/27. Sensitivity of plasma sample was 63.6% among overall, while that was 84.6% in patients with distant metastasis. Eighty-two percent of plasma positive patients at baseline showed molecular response in plasma after two weeks of afatinib treatment. De novo T790M mutation was detected in one patient (2%) from plasma samples. Conclusion: Liquid biopsy seemed to be suitable especially in patients with distant metastasis. Early molecular remission (within two weeks) was observed in 70% of patients.

Keywords: liquid biopsy, afatinib, digital PCR, Prospective study

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Background: This study aimed to investigate the clinical value of bevacizumab in EGFR mutant non-small cell lung cancer (NSCLC) patients who had developed acquired resistance to EGFR-TKIs therapy that manifested as malignant pleural effusion (MPE). Methods: A total of 85 patients were included. Among them, 47 patients received bevacizumab plus continued EGFR-TKIs (B+T) and 39 patients received bevacizumab plus switched chemotherapy (B+C). Results: The curative efficacy rate for MPE in B+T group was significantly higher than that in B+C group (89.4% vs. 64.1%, P = 0.005). Patients in B+T group had longer progression-free survival (PFS) than those in B+C group (6.3 vs. 4.8 months, P = 0.042). While patients with acquired T790M mutation in B+T group had a significantly longer PFS than those in B+C group (6.9 vs. 4.6 months, P = 0.022), patients with negative T790M had similar PFS (6.1 vs. 5.5 months, P = 0.588). Overall survival (OS) was similar between two groups (P = 0.480). In multivariate analysis, curative efficacy was the independent prognostic factor for these patients (HR 0.275, P = 0.047).

POSTER SESSION 3 – P3.028: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/IMMUNOTHERAPY
EGFR CLINICAL - WEDNESDAY, DECEMBER 7, 2016

P3.028-074 BRAIN RADIOTHERAPY WITH EGFR-TKI PLAYS AN IMPORTANT ROLE IN 181 EGFR MUTANT NON-SMALL CELL LUNG CANCER PATIENTS WITH BRAIN METASTASIS
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Background: To perform a retrospective analysis of patients with epidermal growth factor receptor (EGFR)-mutant NSCLC patients who developed brain metastases (BM) to assess the appropriate use of EGFR tyrosine kinase inhibitors (TKIs), and radiation therapy (RT) for symptomatic and asymptomatic BM. Methods: There were 482 patients diagnosed with EGFR mutant NSCLC between June 2006 and December 2015 at Zhejiang Cancer Hospital. Treatment outcomes had been retrospectively evaluated in 181 patients with 132 symptomatic BM and 49 asymptomatic BM. 39 patients received first-line brain RT, 23 patients received delayed brain RT, and 34 patients did not receive brain RT. In all 49 symptomatic BM patients received radiotherapy, except 4 patients were refusal of treatment. There were 45 patients had brain radiotherapy, 39 received WBRT and 6 were SRS. Among 132 asymptomatic brain metastasis patients, 74 received radiotherapy (63 WBRT and 11 SRS). The BM of 26 patients had still stable by the follow-up time. 22 patients did not get information about brain RT after intracranial progression and until the last follow-up. 10 patients were refusal of brain RT treatment. Results: In 49 symptomatic BM patients, 45 received RT including 40 WBRT and 5 SRS. Among 6 SRS, the iPFS for patients treated with SRS and WBRT was 12.4 months and 9.5 months (P=0.895). Median OS in the SRS group was also greater than those in treated with WBRT (37.7 vs 21.1 months) (P=0.194). In the group of 132 asymptomatic BM patients, There were 86 patients who had not received brain radiotherapy before TKI and 46 received RT whether upfront or concurrent TKI. The median OS in the upfront RT group was also longer than in the upfront TKI (24.9 vs 17.4 months)(P=0.035). Further analysis with subgroup to the timing of using radiotherapy, among the 74 patients, 33 underwent concurrent TKI and radiation therapy, 13 were given TKI after failure of first-line radiotherapy plus chemotherapy and 28 patients received radiotherapy after TKI. The iPFS of three groups was 11.1 months, 11.3 months and 8.1 months (P=0.032). The mOS of three groups was 21.9 months, 26.2 months and 17.1 months(P=0.085). Conclusion: The study suggests that the deferral of brain RT may result in inferior OS in NSCLC patients harboring EGFR mutations and asymptomatic BM. For now, the standard-of-care treatment for newly diagnosed BM whether symptomatic or asymptomatic brain metastases should remain upfront RT followed by EGFR-TKI therapy. First-line brain RT may improve long-term survival in EGFR mutation patients.

Keywords: Brain metastases, EGFR TKI, non-small cell lung cancer, radiotherapy

POSTER SESSION 3 – P3.028 ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/IMMUNOTHERAPY
EGFR CLINICAL - WEDNESDAY, DECEMBER 7, 2016

P3.028-075 ADDITION OF BEVACIZUMAB FOR MALIGNANT PLEURAL EFFUSION AS THE MANIFESTATION OF ACQUIRED EGFR-TKI RESISTANCE IN NSCLC PATIENTS

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P3.02B-076 BISPHOSPHONATES ENHANCE EFFECT OF EGFR-TKIS IN NSCLC PATIENTS WITH EGFR MUTATION AND BONE METASTASES
Tao Jiang, Caicun Zhou
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Background: Whether bisphosphonates could enhance the treatment outcome of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) in non-small-cell lung cancer (NSCLC) patients with EGFR mutation and bone metastases (BM) remains controversial. Methods: 251 NSCLC patients with EGFR mutation and BM were identified. As first-line treatment, 44 patients received EGFR-TKIs alone and 56 patients received EGFR-TKIs plus bisphosphonates. Results: Comparing to TKIs alone, EGFR-TKIs plus bisphosphonates had significant longer progression-free survival (PFS: 11.5 vs 10.5 months; HR = 0.64, P = 0.030), but similar overall survival (OS: 20.2 vs 20.8 months; HR = 0.95, P = 0.847) in NSCLC with EGFR mutation and BM. Although the incidence of skeletal-related events in combined treatment group was lower than that in EGFR-TKIs alone group, there is no statistical significance (32.1% vs 45.5%, P = 0.173). Chemotherapy plus bisphosphonates had similar PFS (6.4 vs 6.7 months; HR = 1.09, P = 0.684) and OS (15.5 vs 14.1 months; HR = 0.87, P = 0.486) to chemotherapy alone in patients with EGFR of wild type. In multivariate analysis, EGFR mutation was found to be a significant independent prognostic factor for OS in NSCLC patients with BM (HR = 0.72, P = 0.019).

Conclusion: The addition of bisphosphonates to EGFR-TKIs could enhance the effect of EGFR-TKIs in NSCLC patients with EGFR mutation and BM. Bisphosphonates did not bring additional benefit to chemotherapy in BM patients with EGFR of wild type. EGFR mutation was the significant independent prognostic factor for OS in NSCLC patients with BM.

Keywords: bone metastases, EGFR mutation, EGFR TKI, Non-small-cell lung cancer

Conclusion: Bev+T could be a valuable treatment for NSCLC patients presenting with MPE upon resistant to EGFR-TKIs therapy, especially for those with acquired T790M mutation.

Keywords: bevacizumab, EGFR TKI, EGFR T790M, non-small cell lung cancer
Details of the 22 patients harboring the EGFR T790M mutation are listed in Table 1. The response rate to chemotherapy was 12.5% (best response; 1 PR, 4 SD and 3 PD) and the median time to progression (TTP) was 3.0 months. The response rate to EGFR TKIs treatment was 8.3% (best response; 1 PR, 3 SD and 8 PD), and the median TTP was 2.7 months. Three patients were treated with third generation EGFR TKIs (osimertinib or ASP 8237) and achieved a partial response (TTP; 33.3, 13.6 and 3.5 months, respectively). Conclusion: De novo EGFR T790M mutation is a rare event even in EGFR mutant NSCLC and associated with unfavorable clinical outcome to chemotherapy and EGFR TKIs.

Keywords: non-small cell lung cancer, Epidermal growth factor receptor, T790M, de novo.

POSTER SESSION 3 - P3.02B: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/IMMUNOTHERAPY
EGFR CLINICAL - WEDNESDAY, DECEMBER 7, 2016

P3.028-077 OSIMERTINIB EXPANDED ACCESS PROGRAM FOR PREVIOUSLY TREATED PATIENTS WITH ADVANCED EGFR T790M MUTATION-POSITIVE NSCLC
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Background: The US AZD9291 Expanded Access Program (EAP) was conducted to provide compassionate access to osimertinib for previously treated patients with advanced/metastatic, epidermal growth factor receptor (EGFR) T790M mutation-positive non-small cell lung cancer (NSCLC). Methods: Patients (≥18 years old) with EGFR T790M mutation-positive NSCLC and a WHO Performance Status of 0–2 who had received ≥2 prior lines of therapy that included an EGFR tyrosine kinase inhibitor (TKI) or progressed during EGFR TKI treatment, were eligible. Patients received osimertinib at 80mg oral, once-daily, until dose reduction, discontinuation or EAP completion following FDA approval (November 2015). Patient demographics, T790M testing, safety and tolerability including serious adverse events (SAEs) were collected. Patient response was collected at investigator discretion, but not mandated by the EAP protocol. For required T790M diagnostics, various testing methods were permitted. Results: Osimertinib was provided to 248 EGFR T790M mutation-positive patients through the EAP (May 2015 to November 2015). Of the 244 patients with reported T790M method data, the majority were enrolled based on samples from tissue (n=187) and blood (n=48), whereas others were based on pleural fluid (n=5) or urine (n=4). Use of non-invasive (ie, liquid biopsy) T790M testing varied across the 25 participating sites: 5 sites (20%) enrolled no patients using liquid biopsy, 2 (8%) enrolled all patients based on liquid biopsy, and 17 (72%) enrolled based on different methods. Median age was 65 years old (range, 31–91), 69% of patients were female, and 85% of patients received ≥2 prior cancer treatments. Prior erlotinib therapy was reported in 96% of patients. Starting daily dose of 80mg osimertinib was maintained throughout the study in 238 patients (96%) and reduced to 40mg for patients who received RT followed by icotinib, including WBRT or SRS. 41 patients received icotinib therapy alone. Results: The OS from diagnosis of BM was 27.0 months for the whole cohort (95% CI, 23.9–30.1 months). There was no difference in OS between the RT followed by icotinib group and the icotinib alone group (31.9 vs. 27.4 months, P=0.237), and similar results were found in the SRS subgroup (35.5 vs. 27.9 months, P=0.12). Patients with the EGFR Del19 mutation had a longer OS than patients with the exon 21 L858R mutation (32.7 vs. 27.4, P=0.037). Intracranial progression-free survival (PFS) was improved in the patients who received RT followed by icotinib compared to those receiving icotinib alone (22.4 vs. 13.9 months, P=0.043). The OS from diagnosis of BM was 27.0 months for the whole cohort (95% CI, 23.9–30.1 months). There was no difference in OS between the RT followed by icotinib group and the icotinib alone group (31.9 vs. 27.9 months, P=0.237), and similar results were found in the SRS subgroup (35.5 vs. 27.9 months, P>0.12). Patients with the EGFR Del19 mutation had a longer OS than patients with the exon 21 L858R mutation (32.7 vs. 27.4, P=0.037). Intracranial progression-free survival (PFS) was improved in the patients who received RT followed by icotinib compared to those receiving icotinib alone (22.4 vs. 13.9 months, P=0.043). Conclusion: Patients with EGFR-mutant advanced adenocarcinoma and BM treated with icotinib exhibited prolonged survival. A longer duration of intracranial control was observed with brain RT.

Keywords: lung cancer, icotinib, EGFR, brain metastases.

POSTER SESSION 3 - P3.02B: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/IMMUNOTHERAPY
EGFR CLINICAL - WEDNESDAY, DECEMBER 7, 2016

P3.028-079 EFFECTS OF ICOTINIB WITH AND WITHOUT RADIATION THERAPY ON PATIENTS WITH EGFR MUTANT NON-_SMALL-CELL LUNG CANCER AND BRAIN METASTASES
Yun Fan, Yanjun Xu, Lei Gong, Lulu Miao, Hongyang Lu, Jing Qin, Na Han, Fajun Xie, Guoqing Qiu, Zhiyu Huang
Chemotherapy, Zhejiang Cancer Hospital, Hangzhou/China.

Background: EGFR-TKIs and radiation therapy (RT) are the principal treatment for patients with brain metastases (BM) and EGFR mutant NSCLC. However, the optimal use of brain RT for patients with asymptomatic BM remains undefined. Methods: A total of 152 patients were identified. 56 patients were excluded. Of the remaining 97 patients, 56 patients received upfront RT followed by icotinib, including WBRT or SRS. 41 patients received icotinib therapy alone. Results: The OS from diagnosis of BM was 27.0 months for the whole cohort (95% CI, 23.9–30.1 months). There was no difference in OS between the RT followed by icotinib group and the icotinib alone group (31.9 vs. 27.4 months, P=0.237), and similar results were found in the SRS subgroup (35.5 vs. 27.9 months, P=0.12). Patients with the EGFR Del19 mutation had a longer OS than patients with the exon 21 L858R mutation (32.7 vs. 27.4, P=0.037). Intracranial progression-free survival (PFS) was improved in the patients who received RT followed by icotinib compared to those receiving icotinib alone (22.4 vs. 13.9 months, P=0.043). The OS from diagnosis of BM was 27.0 months for the whole cohort (95% CI, 23.9–30.1 months). There was no difference in OS between the RT followed by icotinib group and the icotinib alone group (31.9 vs. 27.9 months, P=0.237), and similar results were found in the SRS subgroup (35.5 vs. 27.9 months, P>0.12). Patients with the EGFR Del19 mutation had a longer OS than patients with the exon 21 L858R mutation (32.7 vs. 27.4, P=0.037). Intracranial progression-free survival (PFS) was improved in the patients who received RT followed by icotinib compared to those receiving icotinib alone (22.4 vs. 13.9 months, P=0.043). Conclusion: Patients with EGFR-mutant advanced adenocarcinoma and BM treated with icotinib exhibited prolonged survival. A longer duration of intracranial control was observed with brain RT.

Keywords: lung cancer, icotinib, EGFR, brain metastases.

POSTER SESSION 3 - P3.02B: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/IMMUNOTHERAPY
EGFR CLINICAL - WEDNESDAY, DECEMBER 7, 2016

P3.028-080 ANALYSIS OF PATIENT-REPORTED SYMPTOM RESPONSE WITH OSIMERTINIB (AZD9291) TREATMENT FOR ADVANCED NON-SMALL-CELL LUNG CANCER
Suk-Jin hole1, Katja Rudel1, Carolyn Bodnar2, Sarah Fowler2, Tina Rupnik3, Serban Ghiorghiu4
1Department of Oncology, University of Turin, Turin/Italy, 2Astrazeneca, Cambridge/United Kingdom, 3Phastar, London/United Kingdom.

Background: We evaluated whether self-reported symptoms significantly improved in advanced non-small-cell lung cancer patients receiving osimertinib 80mg once-daily and the effect of adjusting by objective tumour response status (ORRS). Methods: In phase II trials (AURA extension, N=201, NCT01802632 and AURA2, N=210, NCT02094261) patients completed the European Organisation for Research and Treatment of Cancer QLQ-LC13. In AURA extension paper-based questionnaires were used every 6 weeks until treatment discontinuation; in AURA2 data were collected electronically weekly for 6 weeks, then every 3 weeks until death. Statistical analyses determined the change from baseline in selected symptoms overall by ORRS. Least squares means (95% CIs) were calculated using linear mixed models for repeated measures. Results: Tables show the change in some symptoms

$S650$
Overall, a significant improvement in symptoms was observed for 6 months with osimertinib treatment, with improvement observed as early as 6 weeks. Patients with OTRS had greater symptom improvement, although this was more apparent in AURA2 than in AURA extension over time. This difference may be explained by symptom collection post-progression in the later trial, AURA2.

Keywords: osimertinib, symptoms, Non-small-cell lung cancer, Patient-reported outcomes

### Least squares mean symptom scores (95% CI)

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<thead>
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<th></th>
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</tr>
</thead>
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</tr>
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<td>(-14.16,8.13)</td>
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</table>

NR, non-responder; R, responder; w, weeks Conclusion: Overall, a significant reduction in symptoms was observed for 6 months with osimertinib.

---

**Table 1.** Symptom change overall/ by OTRS (AURA extension).

<table>
<thead>
<tr>
<th>Least squares mean symptom scores (95% CI)</th>
<th>6w</th>
<th>12w</th>
<th>18w</th>
<th>24w</th>
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<tr>
<td><strong>Cough</strong></td>
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<tr>
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<td>-3.89</td>
<td>-1.36</td>
<td>-1.39</td>
</tr>
<tr>
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<tr>
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<td>13.61</td>
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<td></td>
<td>(17.13,-12.08)</td>
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<td><strong>Dyspnoea</strong></td>
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<td>Total</td>
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<td>-5.31</td>
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<td>Total</td>
<td>-8.12</td>
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<td>(8.04,11.42)</td>
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<td>(12.59,6.78)</td>
<td>(12.87,-6.95)</td>
<td>(11.29,-5.30)</td>
<td>(10.60,-4.49)</td>
</tr>
</tbody>
</table>

NR, non-responder; R, responder; w, weeks Conclusion: Overall, a significant reduction in symptoms was observed for 6 months with osimertinib.
were treated with EGFR-TKIs. Response rates of 1st generation EGFR-TKI with common and uncommon EGFR mutations in Fukuchiyama City Hospital. The effectiveness of EGFR-TKIs (gefitinib, erlotinib, and afatinib) in patients to EGFR-TKI are also unknown. Methods: We analyzed the clinical data and mutations are identified, such as exon 18 G719X mutation, exon 20 S768I mutation which accounts for a large part of 1st and 2nd generation EGFR-TKI resistance, is well known to be detected after failure of prior EGFR-TKI as exon 19 deletions and exon 21 L858R mutation are strong predictors of resistance. But complete responses are rare and all patients progress. We conducted serial RNAseq analyses of EGFR mutant cell lines exposed to gefitinib and osimertinib. We found a rapid induction of gene reprogramming indicative of WNT signaling and EMT signaling that developed within 72 hours of drug exposure and lasted through at least 57 days. Important genes involved included E-cadherin, vimentin, ZEB1&2, axin2, IL8 and others. We therefore elected to determine if inhibitors of Wnt or EMT reprogramming would produce synergistic growth inhibition in EGFR mutant cell lines exposed to osimertinib. Prior clinical studies indicated that the HDAC inhibitors can safely be combined with EGFR-TKIs. Methods: Growth inhibition in the HCC4006 line by osimertinib (10-100nM) in combination with the WNT/beta-catenin inhibitors AZD1366, ICG01, E7449 (30-270nM), WntC59, IWP2-V2, LGK974 (90-810nM), and with the HDAC inhibitors etinostat (30-1000nM), panobinostat (10-50nM) and romdepsin (1-5nM) was assessed by 5 day MTT assays. Growth inhibition by osimertinib (2.5-20nM) + etinostat (60-300nM) was also evaluated in the PC9, HCC827, H3255 and PC7T790M EGFR mutant lines. Analysis of the combined drug effects was by the median-dose effect method using the CalcuSyn program to determine the combination indices (CI). CI values of ≤ 0.75 are indicative of drug synergy. Results: The CI values from combining 30nM osimertinib with the midrange concentration of the Wnt pathway inhibitors and HDAC inhibitors in the HCC4006 line varied from 0.18 to 1.2 and most were ≤ 0.75. The tankyrase inhibitor AZD1366 produced the most synergistic effect with CI = 0.18. CI values of ≤ 0.5 were observed with WntC59 and ICG01. The HDAC inhibitors all produced CI values of ≤ 0.75 with the lowest value of 0.23 for etinostat. CI values of osimertinib combined with panobinostat and romdepsin were 0.51 and 0.73 respectively. CI values for 30nM osimertinib combined with etinostat in the other EGFR mutant cell lines were also synergistic ranging from 0.37 in PC9 to 0.36 in the H3255 line. Synergy was also observed with romdepsin and panobinostat in these lines. Conclusion: The combination of WNT pathway inhibitors or HDAC inhibitors with EGFR-TKIs produce synergistic growth inhibition and may prevent EMT and survival pathways in EGFR mutant lung cancers. Keywords: EGFR-TKIs, Wnt pathway, EMT

Three patients underwent rebiopsy after failure of treatment with afatinib. In two patients with G79X mutation, the tumor disappeared at rebiopsy. In one patient with S768I mutation, new G79X mutation was detected in addition to S768I mutation. Conclusion: Uncommon EGFR mutations could be used as predictors of better response to afatinib, the 2nd generation EGFR-TKI. However, uncommon EGFR mutations are clinically heterogeneous. For instance, our data suggest that smoking be associated with G79X mutation, but not with S768I mutation. Further prospective researches are needed to establish the standard therapy for each uncommon EGFR mutation. Keywords: G79X, S768I, afatinib, uncommon EGFR mutation
Academy of Medical Sciences & Peking Union Medical College, Beijing/China

Background: There is no optimal therapy established for those who have progressed with the Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKI). And some preclinical study indicated that the addition of S-1 to EGFR-TKIs might overcome EGFR-TKI resistance. This study was conducted to investigate the efficacy and safety of the combination therapy of S-1 and EGFR-TKIs for patients failed the previous EGFR-TKI treatments. Methods: All patients with advanced NSCLC were included in this study. The combination therapy of S-1 and EGFR-TKI was effective and well-tolerated for those failed prior EGFR-TKI.

Conclusion: These preliminary data showed that ASP8273 300 mg is generally well tolerated and demonstrated antitumor activity in TKI-naïve Japanese subjects with EGFR mutation-positive NSCLC.

Keywords: NSCLC, ASP8273, EGFR-TKI

POSTER SESSION 3 – P3.02B: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/IMMUNOTHERAPY
EGFR CLINICAL – WEDNESDAY, DECEMBER 7, 2016

Poster 028-087 DOSE ESCALATION STUDY OF CDDP PLUS PEM WITH ERLOTINIB AND BEV FOLLOWED BY PEM WITH ERLOTINIB AND BEV FOR NON-SQ NSCLC HARBORING EGFR MUTATIONS

Mototora Tamiya, Akihiro Tamiami, Takayuki Shiyoyama, Sawa Takeoka, Yujiro Naito, Naoki Omachi, Yohiie Kimura, Naoko Morishita, Hidekazu Suzuki, Norio Okamoto, Katsuyuki Kiura, Masahiro Fujimura, Kazuhiro Nakagawa

Background: The current treatment for advanced non-squamous NSCLC patients without EGFR mutations is platinum doublet chemotherapy. Two phase III trials have demonstrated that cisplatin plus pemetrexed with erlotinib and bevacizumab as a first-line treatment for advanced non-squamous NSCLC patients was superior to cisplatin plus pemetrexed with erlotinib and bevacizumab as a first-line treatment for advanced non-squamous NSCLC patients. Therefore, we performed the present study to further determine the safety and efficacy of the combination of platinum-based chemotherapy with erlotinib and bevacizumab.

Methods: Patients received escalating doses of cisplatin plus pemetrexed with erlotinib and bevacizumab every 3 weeks for 4 cycles. We examined the dose-limiting toxicity (DLT) to determine the maximum tolerated dose (MTD) and recommended dose (RD) of quartet chemotherapy. Results: Ten patients were enrolled. There were no DLTs observed in the first 3 cycles of treatment. Median age was 69 (65-75) years old. 5 patients were men and 5 patients were women. There have not been any evidence-based studies of erlotinib and bevacizumab in combination with platinum-doublet therapy for advanced non-squamous NSCLC patients with EGFR mutations. Therefore, we performed this study to further determine the safety and efficacy of the combination of platinum-based chemotherapy with erlotinib and bevacizumab.

Conclusion: The combination of cisplatin plus pemetrexed with erlotinib and bevacizumab as a first-line treatment for advanced non-squamous NSCLC patients was superior to cisplatin plus pemetrexed with erlotinib and bevacizumab as a first-line treatment for advanced non-squamous NSCLC patients. Therefore, we performed this study to further determine the safety and efficacy of the combination of platinum-based chemotherapy with erlotinib and bevacizumab.

Keywords: NSCLC, ASP8273, EGFR-TKI

Table 3. Tolerability of ASP8273

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<th>Subject</th>
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<th>RD</th>
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<th>RD-</th>
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Poster 028-086 ASP8273 TOLERABILITY AND ANTITUMOR ACTIVITY IN TKI-NAIVE JAPANESE SUBJECTS WITH EGFRMT+ NSCLC: PRELIMINARY RESULTS

Makoto Nishio, Koichi Azuma, Hitohide Hashiyahi, Yoshiaki Hikita, Aki Inoue, Yausu Iwamoto, Satoshi Ikeda, Katsuyuki Kiyuma, Miyako Satouchi, Shunichi Sugiwara, Koji Takeda, Desai Bharadwaj, Anne Keating, Kenji Kira, Kentaro Takezaki, Satoshi Morita, Masahiro Fujukou, Kazuhiro Nakagawa

Background: The current treatment for advanced non-squamous NSCLC patients without EGFR mutations is platinum doublet chemotherapy. Two phase III trials have demonstrated that cisplatin plus pemetrexed with erlotinib and bevacizumab as a first-line treatment for advanced non-squamous NSCLC patients was superior to cisplatin plus pemetrexed with erlotinib and bevacizumab as a first-line treatment for advanced non-squamous NSCLC patients. Therefore, we performed the present study to further determine the safety and efficacy of the combination of platinum-based chemotherapy with erlotinib and bevacizumab.

Methods: Patients received escalating doses of cisplatin plus pemetrexed with erlotinib and bevacizumab every 3 weeks for 4 cycles. We examined the dose-limiting toxicity (DLT) to determine the maximum tolerated dose (MTD) and recommended dose (RD) of quartet chemotherapy. Results: Ten patients were enrolled. There were no DLTs observed in the first 3 cycles of treatment. Median age was 69 (65-75) years old. 5 patients were men and 5 patients were women. There have not been any evidence-based studies of erlotinib and bevacizumab in combination with platinum-doublet therapy for advanced non-squamous NSCLC patients with EGFR mutations. Therefore, we performed this study to further determine the safety and efficacy of the combination of platinum-based chemotherapy with erlotinib and bevacizumab.

Conclusion: The combination of cisplatin plus pemetrexed with erlotinib and bevacizumab as a first-line treatment for advanced non-squamous NSCLC patients was superior to cisplatin plus pemetrexed with erlotinib and bevacizumab as a first-line treatment for advanced non-squamous NSCLC patients. Therefore, we performed this study to further determine the safety and efficacy of the combination of platinum-based chemotherapy with erlotinib and bevacizumab.

Keywords: NSCLC, ASP8273, EGFR-TKI

Table 1. Tolerability of ASP8273

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Poster 032-028 ADVANCED NSCLC CHEMOTHERAPY/TARGETED THERAPY/IMMUNOTHERAPY
EGFR THERAPY – WEDNESDAY, DECEMBER 7, 2016

P3.02B-087 DOSE ESCALATION STUDY OF CDDP PLUS PEM WITH ERLOTINIB AND BEV FOLLOWED BY PEM WITH ERLOTINIB AND BEV FOR NON-SQ NSCLC HARBORING EGFR MUTATIONS

Mototora Tamiya, Akihiro Tamiami, Takayuki Shiyoyama, Sawa Takeoka, Yujiro Naito, Naoki Omachi, Yohiie Kimura, Naoko Morishita, Hidekazu Suzuki, Norio Okamoto, Kyoichi Oshiko, Tomoya Kawaguchi, Shintji Atagi, Tomonori Hiranaka

Background: The current treatment for advanced non-squamous NSCLC patients without EGFR mutations is platinum doublet chemotherapy. Two phase III trials have demonstrated that cisplatin plus pemetrexed with erlotinib and bevacizumab as a first-line treatment for advanced non-squamous NSCLC patients was superior to cisplatin plus pemetrexed with erlotinib and bevacizumab as a first-line treatment for advanced non-squamous NSCLC patients. Therefore, we performed the present study to further determine the safety and efficacy of the combination of platinum-based chemotherapy with erlotinib and bevacizumab.

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Conclusion: The combination of cisplatin plus pemetrexed with erlotinib and bevacizumab as a first-line treatment for advanced non-squamous NSCLC patients was superior to cisplatin plus pemetrexed with erlotinib and bevacizumab as a first-line treatment for advanced non-squamous NSCLC patients. Therefore, we performed this study to further determine the safety and efficacy of the combination of platinum-based chemotherapy with erlotinib and bevacizumab.

Keywords: NSCLC, ASP8273, EGFR-TKI

Table 2. Tolerability of ASP8273

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<th>Subject experiencing ≥ TEAE</th>
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<td>7 (23)</td>
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Furthermore, progression free survival and overall survival were not reached. Conclusion: This quartet chemotherapy was a tolerable and effective regimen, and we determined the combination of cisplatin at 60mg/m² plus 500 mg/m² pemetrexed with 150mg erlotinib and 15mg/kg bevacizumab was RD and the combination cisplatin at 75mg/m² was MTD in chemotherapy-naive advanced non-squamous NSCLC patients harboring EGFR mutations (UMIN000012536).

Keywords: EGFR, non-small cell lung cancer, maintenance therapy, combination chemotherapy

P3.028-088 TKI AS FIRST LINE TREATMENT IN ADVANCED NON-SMALL-CELL LUNG CANCER WITH EGFR MUTATIONS

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Background: Erlotinib and gefitinib are reversible, first-generation, single-targeted tyrosine kinase inhibitors (TKIs) to EGFR/ERBB1 receptor. Testing for epidermal growth factor receptor (EGFR) mutations is recommended in patients with nonsquamous non-small cell lung cancer (NSCLC) or NSCLC not otherwise specified as the mutations are predictive biomarkers of response to EGFR TKI therapy. We aim to assess the real world effectiveness of these agents in the setting of the largest Oncologic Centre in Portugal.

Methods: Retrospective analysis of a consecutive series of patients with stage IIIb/IV NSCLC, EGFR mutated, treated with erlotinib or gefitinib as first line treatment, since January 2012 at Instituto Português de Oncologia do Porto, Portugal. Descriptive statistics were used to describe demographics. Treatment effectiveness was assessed by overall survival (OS) and progression free survival (PFS) calculated by Kaplan-Meier method and treatment adverse events (AEs). Results: Of 86 patients with stage IIIb/IV NSCLC, EGFR mutated, treated with TKI therapy at our center, 64% were female and the mean age was 65.9 years (range 41-85). The majority of patients were non-smokers (80.2%) and the most frequent histology was adenocarcinoma (97.7%). The most commonly found EGFR mutations were deletions in exon 19 and mutation in exon 21. Fifty-one patients (59.3%) received erlotinib as first line treatment. As of May 2016, 39 patients (45.3%) are still on first line treatment, with a median follow-up time of 11 months. Median OS was 24 months (CI 95%: 16.7 – 31.3). The overall response rate (ORR) in the erlotinib group and gefitinib group was 41.2% and 34.3%, respectively, with no significant difference between groups (p value 0.652). Overall median PFS was 10 months (CI95%: 7.4 – 12.6), being higher in the erlotinib treatment group (11 versus 7 months). Ten patients in the erlotinib group required dose reductions because of drug related toxic effects, 9 because of rash grade 3 and 1 because of hepatotoxicity. One patient in the gefitinib group suspended treatment because of arthritis. Diarrhea was the second most frequent toxicity related to TKIs (38.4%). Conclusion: Based on our experience, real world effectiveness of erlotinib and gefitinib as first line treatment, with a median follow-up time of 11 months. Median OS was 24 months (CI 95%: 16.7 – 31.3). The overall response rate (ORR) in the erlotinib group and gefitinib group was 41.2% and 34.3%, respectively, with no significant difference between groups (p value 0.652). Overall median PFS was 10 months (CI95%: 7.4 – 12.6), being higher in the erlotinib treatment group (11 versus 7 months). Ten patients in the erlotinib group required dose reductions because of drug related toxic effects, 9 because of rash grade 3 and 1 because of hepatotoxicity. One patient in the gefitinib group suspended treatment because of arthritis. Diarrhea was the second most frequent toxicity related to TKIs (38.4%).

Keywords: advanced non-small-cell lung cancer, Tyrosine kinase inhibitors, EGFR mutations

P3.028-089 TREATMENT OF NSCLC PATIENTS WITH MALIGNANT PLEURAL EFFUSION HARBORING EXON 19 AND 21 EGFR MUTATIONS AFTER FIRST-LINE AND SECOND-LINE TKIS

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Background: Recent studies demonstrated a significantly increased frequency of epidermal growth factor receptor (EGFR) gene mutations in non-small cell lung cancer (NSCLC) patients with malignant pleural effusions (MPEs). However, the sensitivity of tyrosine kinase inhibitors (TKIs) in NSCLC patients with MPE for different EGFR mutations was less reported. The purpose of this study is to investigate the effect of first-line and second-line EGFR-TKIs in the treatment of NSCLC with MPEs harboring exon 19 deletion and L858R mutation. Methods: From 2010 to 2015, 203 NSCLC patients with MPEs harboring EGFR mutation treated with EGFR-TKIs were reviewed.

The efficacy were evaluated with Pearson chi-square or Fisher’s exact tests, Log-rank test and Cox proportional hazards model. Results: The objective response rate (ORR) and disease control rate (DCR) for patients treated with first-line and second-line EGFR-TKIs were 21.9%, 91.4% and 74.7%, 85.3%, respectively. The overall median PFS and OS of enrolled NSCLC patients with MPE were 9.3 months (95% CI, 8.4-10.2 months), 20.9 months (95% CI, 18.9-22.9 months) after first-line TKIs, and 7.6 months (95% CI, 6.6-8.6 months), 15.3 months (95% CI, 13.6-15.9 months) after second-line TKIs, respectively. The exon 19 deletion arm had a longer median PFS (9.4 vs. 7.1 months, p=0.03) and OS (16.8 vs. 13.8 months, p=0.03) compared with the L858R mutation arm after second-line TKIs. ECOG PS (PFS: P=0.004; OS: P=0.01) and TNM stage (PFS: P=0.001; OS: P=0.002) were independent predictors of PFS and OS for NSCLC patients with MPE treated by first-line TKIs. ECOG PS (OS: P=0.01) (PFS: P=0.004; OS: P=0.001), TNM stage (OS: P=0.014; OS: P=0.007) and exon 19 deletions (PFS: P=0.02; OS: P=0.02) were related to a longer PFS and OS for patients treated with second-line TKIs. Gender was also an independent predictor of OS (p=0.04) for patients treated with second-line TKIs. There was no significant difference on side effects between NSCLC patients with ex19 and 21 mutations in the first or second-line EGFR-TKIs. Conclusion: EGFR genotype was an independent predictor of PFS and OS. No significant side effects differences between the two mutation groups was observed for first or second-line EGFR-TKIs. This study demonstrated that EGFR mutations are significant predictors for advanced NSCLC patients with MPE receiving second-line EGFR-TKIs treatment.

Keywords: non-small cell lung cancer, malignant pleural effusion, Epidermal growth factor receptor, Tyrosine kinase inhibitors

P3.028-090 PEMETREXED VERSUS GEFITINIB IN EGFR MUTATION POSITIVE LUNG CANCER: RESULTS OF A PHASE 3 STUDY FROM INDIA

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Background: This study has been designed to confirm the efficacy of gefitinib and pemetrexed combination chemotherapy as first-line treatment for advanced EGFR Mutation status positive adenocarcinoma lung. Methods: This was an open label, randomised, parallel group study comparing Gefitinib (250 mg OD daily) with Pemetrexed (either Cisplatin 75 mg/m² or Carboptin AUC-5) and Pemetrexed (500 mg/m²) doublet intravenous chemotherapy regimen (induction of 4-6 cycles followed by maintenance) in patients with stage IIIb or stage IV adenocarcinoma lung who have confirmed to be EGFR activating mutation-positive in the first line setting. The primary endpoint for the study is progression free survival (PFS). Patients underwent axial imaging for response assessment on D42, D84, D126 and subsequently every 2 months till progression. Patients were followed up till death. For an estimated 50% improvement in progression free survival, with 80% power and 5% type one error, number of patients required will be 260. We expect a 5% dropout rate, which required 290 patients to be randomized. Results: The median PFS in gefitinib arm was 8.433 months (95% CI: 6.322-10.535) while it was 5.6 months (95% CI: 4.207-6.993) in pemetrexed arm (p value-0.000, log rank test). The adjusted hazard ratio was 0.661 (95% CI 0.513-0.852) . The impact of gefitinib was a significant difference in overall survival between the 2 arms.

Variable Subgroup HR 95%CI HR P value
Age Below 65 years 0.66 0.50-0.86 0.003
Above 65 years 0.35 0.18-0.68 0.002
Gender Male 0.66 0.47-0.92 0.014
Female 0.66 0.45-0.97 0.037
Smoking Smoker 0.60 0.34-1.04 0.071
Non smoker 0.60 0.45-0.79 0.000
Oral tobacco use Yes 0.62 0.41-0.92 0.018
No 0.57 0.41-0.79 0.001
POSTER SESSION 3 - P3.02B: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/IMMUNOTHERAPY
EGFR CLINICAL - WEDNESDAY, DECEMBER 7, 2016

P3.02B-091 LIVER METASTASES IS THE NEGATIVE PREDICTIVE FACTOR FOR FIRST-LINE EGFR TKI THERAPY IN NSCLC PATIENTS WITH EGFR MUTATION
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Background: Whether liver metastases (LM) could predict the treatment outcome of patients with non-small-cell lung cancer (NSCLC) and epidermal growth factor receptor (EGFR) mutation receiving first-line EGFR tyrosine kinase inhibitors (TKIs) remains controversial. Methods: A total of 598 patients with advanced NSCLC receiving EGFR detection were included. 99 NSCLC patients had LM and 56 of them with EGFR mutation received EGFR-TKIs as first-line therapy. Results: In EGFR mutation group, patients with LM had shorter progression-free survival (PFS) (7.4 vs. 11.8 months, P = 0.0002) and overall survival (OS) (20.8 vs. 31.5 months, P = 0.0587) compared to patients without LM. Cox proportional hazards model. Results: A total of 184 NSCLC patients with LM were included and 96 patients with LM NSCLC with EGFR mutation were included. Conclusion: The impact of gefitinib on progression free survival in different subgroups. The study confirms superiority of gefitinib against the the most active chemotherapy regimen of pemetrexed platinum in EGFR mutated NSCLC patients.

Keywords: EGFR mutation, NSCLC, Adenocarcinoma, gefitinib

Table 1: Impact of gefitinib on progression free survival in different subgroups. The study confirms superiority of gefitinib against the the most active chemotherapy regimen of pemetrexed platinum in EGFR mutated NSCLC patients.

<table>
<thead>
<tr>
<th>ECOG PS</th>
<th>PFS</th>
<th>OS</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>PS0-1</td>
<td>0.62</td>
<td>0.48-0.82</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>PS2</td>
<td>0.51</td>
<td>0.23-1.10</td>
<td>0.087</td>
<td></td>
</tr>
<tr>
<td>Presence of liver metastasis</td>
<td>Yes</td>
<td>0.55</td>
<td>0.33-0.91</td>
<td>0.020</td>
</tr>
<tr>
<td>No</td>
<td>0.63</td>
<td>0.48-0.85</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>Presence of brain metastasis</td>
<td>Yes</td>
<td>0.56</td>
<td>0.30-1.06</td>
<td>0.073</td>
</tr>
<tr>
<td>No</td>
<td>0.61</td>
<td>0.46-0.80</td>
<td>0.000</td>
<td></td>
</tr>
</tbody>
</table>

Conclusion: Liver metastases is not only the negative predictive factor for first-line EGFR-TKIs therapy in NSCLC patients with EGFR mutation but also predicts poor effect of chemotherapy in NSCLC patients with EGFR wild type.

Keywords: non-small cell lung cancer, Liver Metastasis, EGFR mutation, TKI

POSTER SESSION 3 - P3.02B: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/IMMUNOTHERAPY
EGFR CLINICAL - WEDNESDAY, DECEMBER 7, 2016

P3.02B-092 CENTRAL NERVOUS SYSTEM (CNS) RESPONSES TO OSIMERTINIB IN BRAIN METASTASES FROM LUNG CANCER (NSCLC) WITH T790M: EFFECTIVENESS OF THE 80 MG DOSE
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Background: Patients with progressive CNS metastases from NSCLC who fail radiation therapy (RT) have a poor prognosis and short survival. Systemic chemotherapy is not very effective in controlling CNS metastases that failed RT. Patients with EGFR mutated NSCLC have a higher incidence of CNS metastases on presentation, and during the course of their illness. First and second generation tyrosine kinase inhibitors (TKI) at standard or pulse doses, may produce some clinically significant responses in the brain. Osimertinib is a potent irreversible EGFR TKI selective for activating EGFR and T790M resistance mutations. It has improved CNS penetration compared to earlier generations TKI. Previous reports have demonstrated the activity of osimertinib in the CNS at 160 mg. We report two patients who had failed RT treatment in the brain, who responded very well to the standard dose of osimertinib at 80 mg. Methods: Retrospective review of the charts of two patients was performed. Results: A 41-year old man diagnosed with metastatic adenocarcinoma of the lung with bilateral pulmonary nodules and 3 small brain micro metastases in April 2014. His lung biopsy revealed an EGFR Del 19. He was treated with erlotinib and later received icotinib with an excellent response that lasted 11 months. Progressive brain metastases developed in May 2015 and treated with whole brain RT (WBRT). On WBRT, Osimertinib was prescribed and the patient responded well to WBRT. Osimertinib was continued on subsequent WBRT with brain control. He was continued on Osimertinib for 4 months and developed progression in the lungs. Repeat Guardant 360 revealed an EGFR T790M. He was not a candidate for additional RT. He was started on osimertinib at 80 mg in December 2015. Two months later, brain MRI revealed near complete resolution of the lesions, PET scan showed a significant response. Five months later, brain MRI remains negative and he remains in near complete systemic remission. An 84-year old female was diagnosed with multiple brain lesions in January 2015. Work up revealed a right lung mass, biopsy showed adenocarcinoma. She received WBRT. Blood-based cell-free DNA assay (Guardant 360) revealed an EGFR Del 19. She was treated with Erlotinib for 4 months and developed progression in the lungs. Repeat Guardant 360 revealed an EGFR T790M. Osimertinib 80 mg was started. She remains alive at 18 months with an excellent response in the brain. Conclusion: These two cases highlight the significant activity of osimertinib in the CNS at the standard 80 mg dose. Prospective studies should confirm this finding.

Keywords: osimertinib, T790M, EGFR mutation, CNS metastases

POSTER SESSION 3 - P3.02B: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/IMMUNOTHERAPY
EGFR CLINICAL - WEDNESDAY, DECEMBER 7, 2016

P3.02B-093 ZOLEDRONIC ACID ENHANCES THE EFFECTS OF ICOTINIB ON NON-SMALL CELL LUNG CANCER PATIENTS WITH BONE METASTASES
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Background: Epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKIs) are widely used as molecularly targeted drugs for the treatment of non-small cell lung cancer (NSCLC), with icotinib being one such EGFR-TKI. Bone metastases occur in 30–40% of patients with advanced non-small cell lung cancer (NSCLC). Zoledronic acid is a third-generation bisphosphonate, and is effective for the reduction of the skeletal-related events (SREs). In addition, some reports have described the possibility of direct and indirect antitumor effects of zoledronic acid. However, most of these studies are preclinical research or combination with chemotherapy. Methods: We retrospectively analyzed data of 184 patients treated with zoledronic acid and icotinib. 40 (21.5%) patients were with EGFR mutations (35 with deletions within exon 19, 6 with
L858R messenger mutation in exon 21 and with G719X mutation in exon 18). Median PFS of all patients during icotinib treatment was 10.7 months. The median overall survival (OS) time for all patients was 24.3 months. The PFS in 21-year and ≤1-year zolendronic acid group was 12.1 months and 10.2 months (P = 0.351). And the PFS in the group of 2 years zolendronic acid was longer than the group of ≥2 years zolendronic treatment (12.2 versus 10.5 months, P=0.175). The cumulative incidences of bone pain had not increased during 1 year zolendronic acid treatment than before ZOL treatment (31.0% versus 45.1%). 39 of the 92 patients in ≥1-year zolendronic acid treatment (39.1%) and 26 of the 92 patients in <1-year zolendronic acid (26.1%) experienced SREs before zolendronic acid treatment (P = 0.059). During zolendronic acid treatment, the incidence rate of SREs in group of ≥1-year and <1-year were 17.4% (16/92) and 13.0% (12/92), respectively. Conclusion: Hence, combined treatment of EGFR-TKI with zolendronic acid may have a more effective for NSCLC with bone metastases, particularly in EGFR mutation patients.

Keywords: non-small cell lung cancer; bone metastases; Zoledronic; SREs

**POSTER SESSION 3 – P3.02B: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/ IMMUNOTHERAPY EGFR RES – WEDNESDAY, DECEMBER 7, 2016**

**P3.028-094 REBIOPSY POST PROGRESSION IN EGFR MUTATED LUNG CANCER**

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Background: Post progression on treatment with chemotherapy/TKIs, adenosarcoma of the lung may transform histologically and or gain/loss receptor function Methods: This was a post hoc analysis of a phase 3 randomized study. Classic activating EGFR mutation positive patients warranting palliative chemotherapy were enrolled in this study and randomized to either gefitinib or permetrexed carboplatin doublet. The data regarding rebiopsy post progression on first line was collected for this analysis and descriptive analysis was performed Results: We had 290 patients out of which 214 patients had progressed. The initial EGFR mutation status of these patients was exon 19 (85 patients (39.7%), exon 19 in 124 patients (57.9%), and exon 18 in 15 patients (2.4%). The 4 most common reasons for not doing the biopsy following progression were ; biopsy not offered in 57 patients, no measurable or biopsiable lesion in 13 patients, poor PS in 13 patients, for the biopsy at initial treatment, and other reasons in 13 patients. In 166 evaluable for response: median age, 60.0 years; female, 69%; Asian, 98%; never smokers, 78%; PS 0/1, 15%/85%; EGFR Exon 19 and Exon 21 mutations. Following positive outcomes from recent Phase I and II trial, osimertinib is now recommended for patients with T790M mutation-positive advanced non-small cell lung cancer (aNSCLC). Methods: AURA17 (NCT02442349) is an open-label, single arm, Phase II study investigating the efficacy and safety of osimertinib in Asian-Pacific patient population with EGFR T790M mutation-positive locally advanced or metastatic NSCLC who had progressed following EGFR-TKI therapy or EGFR-TKI chemotherapy. T790M-positive status was confirmed via central testing of biopsy samples after the cobas EGFR Mutation Test. Inclusion required measurable disease, at least one post-EGFR-TKI treatment line, and tolerability. Results: As of 4 March 2016 data cut-off, 171 patients were enrolled, with 166 evaluable for response: median age, 60.0 years; female, 69%; Asian, 98%; never smokers, 78%; PS 0/1, 15%/85%; EGFR Exon 19 and L858R mutations, 64% and 34% patients, respectively; second/third-line, might vary spatiotemporally and consequently hinder the initiation and clinical efficacy of third generation EGFR TKIs. Till now, the spatiotemporal traces of T790M under treatment pressure have not been fully elucidated. Methods: We retrospectively analyzed 790M status of 93 patients who underwent multiple (≥2) rebiopsies after acquired resistance to first or second generation EGFR TKIs from 2010 to 2015 in Guangdong General Hospital. Patients underwent synchronous rebiopsies at the same lesion or different sites, rebiopsies at the same site or different lesions were enrolled to evaluate the temporal and spatiotemporal T790M heterogeneity respectively. Results: T790M detection was performed by SNAPSHOT or Amplification Refraction Mutation System (ARMS). Plasma EGFR was detected by ARMS. Results: A total of 99 evaluations were performed with 6 of 93 enrolled patients underwent both synchronous and heterochronous rebiopsies. Among 20 patients who underwent synchronous rebiopsies at the same lesion, 13 revealed T790M heterogeneity. Among 17 patients who had paired tissue and plasma rebiopsies, 8 showed T790M heterogeneity. Spatial T790M heterogeneity rate was 57% (21/37) in general. 33% (10/30) patients who received heterochronous rebiopsies at the same lesion revealed temporal T790M heterogeneity. Spatiotemporal T790M heterogeneity was observed in 53% (19/37) of patients who received heterochronous multiple sites rebiopsies. Of abovementioned patients with heterochronous T790M heterogeneity, T790M status in 67% (18/27) switched from negative to positive under after chemotherapy or combination of EGFR TKIs in 33% (9/27) switched from positive to negative after chemotherapy or combined regimens of chemotherapy and EGFR TKIs. Conclusion: T790M status could vary spatiotemporally at a ratio of 3:2. In patients with acquired resistance to previous EGFR TKIs. Repeated rebiopsies both at the same lesion and various lesions might be valued particularly in T790M-negative cases in this subset of patients.

Keywords: Acquired resistance, EGFR TKIs, spatiotemporal heterogeneity, T790M
32% ± 68%; median treatment exposure, 5.6 months. Confirmed ORR and DCR (95% CI) by BICR were 60% (52, 68) and 88% (82, 92), respectively. DoR and PFS are not calculable as data is immature. Causally-related adverse events (AEs) grade ≥3 were reported in nine (5%) patients. AEs leading to dose interruption or dose reduction occurred in seven (4%) and two (1%) patients, respectively. Six (4%) patients discontinued treatment due to AEs, two (1%) causally-related AEs as assessed by investigator. The most commonly reported AEs (≥4; [grade ≥3]) were diarrhea (29%; [0]), rashes and acne (grouped terms) (20%; [0]), and dry skin (grouped terms) (17%; [1]), respectively. Interstitial lung disease-like events were reported in three (2%) patients.

Conclusion: AURA17 demonstrated clinical efficacy of osimertinib in Asia-Pacific patients with EGFR T790M mutation-positive aNSCLC, with an ORR of 60% and DCR of 88% that are comparable to global Phase II trials. Osimertinib was well tolerated, with a low frequency of AEs grade ≥3. No new safety signals were observed and the pattern of AEs was consistent with global studies.

Keywords: EGFR-TKI, T790M, osimertinib (AZD9291), EGFR mutation

P3.028-097 EXPERIENCE OF RE-BIOPSY (BIOPSY AT PROGRESSION) OF EGFR MUTANT NON- SMALL CELL LUNG CANCER PATIENTS IN JAPAN: A RETROSPECTIVE STUDY

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Background: To confirm mechanisms of resistance to targeted therapy and to evaluate future treatment strategy, biopsy at progression is important and necessary. Since biopsy at progression is not standard of care, we investigated real-world clinical practice in Japanese patients with non-small cell lung cancer (NSCLC) patients harboring the epidermal growth factor receptor (EGFR) gene mutation.

Methods: This was a retrospective, multi-center, observational study in Japan. EGFR mutation positive NSCLC patients who developed disease progression after treatment by EGFR tyrosine kinase inhibitor (TKI) were enrolled. The primary objective was the success rate of re-biopsy (biopsy at progression). The secondary objectives were differences of between the two methods. The success rate of re-biopsy was 79.5% (314/395) and complications associated with re-biopsy. Results: 395 patients were enrolled prospectively. T790M mutation was determined in plasma samples by ARMS and ddPCR assay. Disease failure site was defined into three types of chest limited (CP), brain limited (BP) and extensive progression (EP).

Conclusion: AURA17 demonstrated clinical efficacy of osimertinib in Asia-Pacific patients with EGFR-TKI therapy. Osimertinib was well tolerated, with a low frequency of AEs grade ≥3. No new safety signals were observed and the pattern of AEs was consistent with global studies. Re-biopsy for the EGFR TKI failure NSCLC patients is feasible in Japan.

Keywords: T790M, EGFR, NSCLC, re-biopsy

P3.028-098 PLASMA T790M MUTATION ASSOCIATES WITH EXTENSIVE PROGRESSION IN NON-SMALL CELL LUNG CANCER WITH ACQUIRED RESISTANCE TO EGFR INHIBITORS

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Background: T790M mutation is a major mechanism for clinical failure in non-small cell lung cancer (NSCLC) patients with EGFR-TKI therapy. Acknowledgement of its frequency/abundance and its correlation with clinical characteristics will be significant importance for the management of those patients in clinical practice and future trial design. Due to the difficulty of rebiopsy, plasma ctDNA is an ideal biopsy for detection of T790M mutation.

Methods: 314 patients with advanced or recurrent NSCLC who had progressed during EGFR-TKIs treatment were enrolled prospectively. T790M mutation was determined in plasma samples by ARMS and ddPCR assay. Disease failure site was defined into three types of chest limited (CP), brain limited (BP) and extensive progression (EP). The T790M mutation status was analyzed for their correlations with failure site and clinical characteristics. Results: T790M mutations were detected in 30.9% and 46.8% of the patients by ARMS and ddPCR, respectively. The concordance rate was 78.3% between two methods. Compared to patients with CP and BP, EP patients showed significant higher rate for T790M mutation determined by both ARMS and ddPCR (73.8% and 54.7%, p < 0.001). In T790M positive population, the median T790M abundance was 1.2% (range, 0.04%-70.3%), and the median abundance of CP, BP and EP was 0.66%, 1.52%, and 2.61%, respectively (p = 0.062). When adjusting for TKI response, worse PFS was found correlated with the plasma T790M mutation by ddPCR.

Conclusion: Plasma T790M status correlates the extensive progression in NSCLC patients with EGFR-TKI therapy, which may provide the important ancillary information for treatment decision-making.

Keywords: ctDNA, ddPCR, TKI resistance, T790M

Poster Session 3 - P3.028 Advanced NSCLC & Chemotherapy/Targeted Therapy/Immunotherapy

Abstracts

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Poster Session 3 - P3.028 Advanced NSCLC & Chemotherapy/Targeted Therapy/Immunotherapy

Wednesday, December 7, 2016
Abstracts

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Background: The third generation of TKI showed promising activities in patients with acquired T790M mutation. However, many patients in this setting are unable to undergo biopsy due to limited tissue availability and procedural feasibility. Mutation detection in plasma has shown promises to conquer the clinical challenging of re-biopsy, with advantage of non-invasiveness and accessibility. Here, we chose and evaluated the performance of three methods, amplification refractory mutation system (ARMS), modified amplification refractory mutation system (SuperARMS), and droplet digital PCR (ddPCR), to assess their concordance and feasibility for the detection of mutations in plasma samples. Methods: This study was performed between March 2015 and March 2016. Patients were considered eligible and were enrolled in this study if they met the following criteria: 1) histologically confirmed stage IIIB/IV NSCLC; 2) clinical resistance to first-generation EGFR-TKIs according to Jackman's criteria. Blood samples were collected within 14 days after TKI resistance. Each sample was simultaneously detected by three methods. Results: In total, 169 patients were enrolled. 54.4% were female and 72.2% were diagnosed as stage IV; 97.6% were adenocarcinoma. The rates of patients in response to EGFR TKI treatment were 35.5% for stable disease, 51.2% for partial response and 12.4% for complete response, respectively. T790M mutations were detected in 54 of 169 (32.0%) samples by ARMS, 33 of which simultaneously carried exon19 deletions and 21 of which carried L858R. For SuperARMS assay, 59 (34.9%) samples were detected T790M mutation and 110 (65.1%) were not detected. ddPCR results showed that 61 (36.1%) samples were with detectable T790M mutation and 108 (63.9%) samples were detected with wildtype T790M. T790M abundance ranged from 0.04% to 38.2%. The median T790M abundance was 0.15% for total samples and 2.98% for T790M mutation samples. The overall concordance was 81.1% (137/169) among ARMS, SuperARMS, and ddPCR. The crude and adjust agreement between ARMS and SuperARMS was 86.7% and 86.1%, 88.8% and 87.7% between ARMS and ddPCR, 85.8% and 84.5% between SuperARMS and ddPCR, respectively. We also found that detection of T790M with ddPCR showed a sensitivity of 94.6% (95%CI: 90.97-95.7) and a specificity of 59.9% (95%CI: 51.2-67.9) when took ARMS as reference. Conclusion: Liquid biopsy showed promises with advantage of non-invasiveness and accessibility. T790M detection based on plasma circulation tumor DNA showed high concordance. Compared with non-digital platforms, ddPCR showed higher sensitivity and provided both frequency and abundance information, which might be important for treatment decision-making.

Keywords: amplification refractory mutation system, T790M, TKI resistance, droplet digital PCR

P3.02B-101 EGFR T790M RESISTANCE MUTATION IN NSCLC: REAL-LIFE DATA OF AUSTRIAN PATIENTS TREATED WITH OSIMERTINIB

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Background: Somatic mutations in the epidermal growth factor receptor (EGFR) are detected in approximately 13% of the Austrian non-small cell lung cancer (NSCLC) patients. The EGFR T790M mutation located on Exon 20 is the most common mechanism of drug resistance to EGFR tyrosine kinase inhibitors (TKI) in these patients. The mutation can be detected by liquid biopsy. Osimertinib (AZD9291), a 3rd generation EGFR-kinase inhibitors (TKI) in these patients. The mutation can be detected by real-time PCR, but the sensitivity and specificity is unknown. Osimertinib treatment were 35.5% for stable disease, 51.2% for partial response and 12.4% for complete response, respectively. T790M mutations were detected in 54 of 169 (32.0%) samples by ARMS, 33 of which simultaneously carried exon19 deletions and 21 of which carried L858R. For SuperARMS assay, 59 (34.9%) samples were detected T790M mutation and 110 (65.1%) were not detected. ddPCR results showed that 61 (36.1%) samples were with detectable T790M mutation and 108 (63.9%) samples were detected with wildtype T790M. T790M abundance ranged from 0.04% to 38.2%. The median T790M abundance was 0.15% for total samples and 2.98% for T790M mutation samples. The overall concordance was 81.1% (137/169) among ARMS, SuperARMS, and ddPCR. The crude and adjust agreement between ARMS and SuperARMS was 86.7% and 86.1%, 88.8% and 87.7% between ARMS and ddPCR, 85.8% and 84.5% between SuperARMS and ddPCR, respectively. We also found that detection of T790M with ddPCR showed a sensitivity of 94.6% (95%CI: 90.97-95.7) and a specificity of 59.9% (95%CI: 51.2-67.9) when took ARMS as reference. Conclusion: Liquid biopsy showed promises with advantage of non-invasiveness and accessibility. T790M detection based on plasma circulation tumor DNA showed high concordance. Compared with non-digital platforms, ddPCR showed higher sensitivity and provided both frequency and abundance information, which might be important for treatment decision-making.

Keywords: amplification refractory mutation system, T790M, TKI resistance, droplet digital PCR

POSTER SESSION 3 – P3.02B: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/ IMMUNOTHERAPY EGFR RES.

WEDNESDAY, DECEMBER 7, 2016

P3.02B-100 COMPARISON OF THREE T790M TESTING METHODS FOR THE DETECTION OF NON-SMALL CELL LUNG CANCER AFTER TYROSINE KINASE INHIBITOR FAILURE

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Introduction: The PK analysis set included 25 patients: 6 were excluded due to prior treatment with an osimertinib-like substance or a T790M-directed EGFR-TKI. Osimertinib exposure increased approximately dose-proportionally after single and multiple dosing, similar to previous global studies. 29 (94%) patients experienced at least one adverse event (AE), 3 patients experienced an AE of Grade ≥3; no patients discontinued treatment due to AEs. The most common AEs were: diarrhea (32%), white blood cell decreased (23%), neutrophil count decreased (19%), dry mouth and erythema (19%) (all partial responses) in T790M mutation-positive subgroup was 36% for Cohort 1 (6/11, 95% CI:11.6, 69) and 67% for Cohort 2 (10/15, 95% CI:38, 88). Conclusion: Osimertinib PK in the AURA18 Chinese patient population is consistent with the global population and supports 80 mg once-daily dosing.

Clinical benefit and a tolerable safety profile were demonstrated.

<table>
<thead>
<tr>
<th>After single dose</th>
<th>Cohort 1</th>
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<td>Cmax, nmol/L (CV%)</td>
<td>103.8 (79.2)</td>
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<td>AUC0-C4 amounts, ng·h/mL (CV%)</td>
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<td>AUC0-C4, ng·h/mL (CV%)</td>
<td>8232 (55.8)</td>
<td>10260 (33.1)</td>
</tr>
<tr>
<td>CL/F ± SD</td>
<td>14.3 ± 7.7</td>
<td>16.45 ± 6.1</td>
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<tr>
<td>t1/2, h ± SD</td>
<td>39.24 ± 5.0</td>
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<td>AUC0-C4 amounts, ng·h/mL (CV%)</td>
<td>6509 (82.6)</td>
<td>9570 (35.9)</td>
</tr>
<tr>
<td>CL/F ± SD</td>
<td>15.7 ± 0.5</td>
<td>17.7 ± 0.1</td>
</tr>
</tbody>
</table>

Keywords: Pharmacokinetics, Osimertinib, EGFR-TKI, T790M
with an EGFR TKI. The T790M mutation status was assessed by re-biopsy and/or liquid biopsy. For liquid biopsies, blood samples were collected in EDTA-containing vacutainer tubes and processed within 2 hours after collection. Cell-free plasma DNA was extracted by using the QIAamp circulating nucleic acid kit (Qiagen) according to the manufacturer’s instructions. Mutation status was assessed with QX-100™ Droplet Digital™ PCR System (Bio-Rad). Results: The T790M mutation status was assessed in 48 patients by liquid biopsy only and in 13 patients by re-biopsy of the tumor. In 21 patients the T790M mutation was detected by both methods. 70 (85%) patients showed a clear clinical and radiographic response. Out of these, 70, 14 (17%) patients reached a complete remission, 56 (68%) patients showed partial response and in 5 (6%) patients, a stable disease after treatment with osimertinib was observed. Five patients had symptomatic brain metastasis initially without any further option of local treatment, and showed a clear clinical benefit and a partial remission radiographically. Osimertinib was well tolerated. No clinically relevant significant side effects were reported. Conclusion: Osimertinib was highly active in our patients, while showing good safety profile. Therefore, re-biopsy or liquid biopsy should be performed in clinical routine to detect the T790M mutation. With the above described method, liquid biopsy could replace re-biopsy in clinical practice in the future.

Keywords: T790M, osimertinib, TKI resistance, Liquid Biopsy Re-biopsy

P3.02B-103 IDENTIFICATION OF ON-TARGET MECHANISMS OF RESISTANCE TO EGFR INHIBITORS USING CTDNA NEXT-GENERATION SEQUENCING

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Background: Osimertinib (OSM) is a third-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) recently approved for use in EGFR T790M-positive non-small cell lung cancer (NSCLC) with a 65-70% response rate. However, patients invariably develop resistance to OSM, in ~30% of cases due to an acquired EGFR C797S mutation. Understanding additional, non-C797S resistance mechanisms will be critical to developing new therapeutic approaches. Here, we describe a case of T790M-positive NSCLC with progression under OSM, genotyped using cell-free circulating tumor DNA (ctDNA) next-generation sequencing (NGS). Methods: A 68-year-old male with EGFR L858R-mutant metastatic NSCLC whose disease progressed despite multiple lines of EGFR inhibitors (erlotinib, afatinib, cetuximab/afatinib) and chemotherapy was found to be T790M-positive, and initiated on OSM. Initial staging scans revealed progressive disease. 7 months later, ctDNA testing was performed with a highly sensitive and ultra-specific 70-gene NGS panel (Guardant360™) that includes all EGFR exons and amplons on all EGFR single nucleotide variants, indels, and amplification. Results: Twelve somatic alterations were identified, including 7 mutations in EGFR. The T790M mutation was found to have an allele fraction of 10.1%, and the C797S mutation was not detected. Conclusion: Deep sequencing of ctDNA can reveal the global landscape and evolution of resistance mutations within a patient’s tumor. The T790M and C797S mutations were predominantly in cis configuration, underscoring the importance of developing new EGFR TKIs. The role of L792H and L792F, and F795C is currently unknown. These mutations impinge on the ATP-binding pocket, which could be a potential structural resistance mechanism. Further studies are needed to validate and functionally characterize these candidate resistance mutations.

Keywords: Resistance, ctDNA, EGFR TKI

P3.02B-104 REBIOPSY FOR PATIENTS WITH NON-SMALL-CELL LUNG CANCER AFTER EPIDEMIAL GROWTH FACTOR RECEPTOR TYROSINE KINASE INHIBITOR FAILURES

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Background: All non-small cell lung cancer patients (NSCLC) with mutant epidermal growth factor receptor (EGFR) eventually develop resistance to EGFR tyrosine kinase inhibitors (TKIs). Rebiopsy and retesting plays important role in clinical application for exploring resistance mechanisms and determining further therapy strategies. This retrospective study was performed to determine the performance of patients who underwent rebiopsy and retesting, and the rebiopsy and retesting effect on clinical strategies and patients prognosis. Methods: From October 2011 to March 2016, patients with advanced NSCLC who developed resistance to EGFR-TKIs were included into this study. EGFR mutation detection were performed by ARMS PCR in
our institution. Results: A total of 539 patients were enrolled in this study with a median progression-free survival time (PFS) of 11.1 months according to RECIST criteria. In all, 297 (55.1%) patients underwent rebiopsy for 178 computed tomography (CT)-guided needle biopsies, 87 serous cavity effusion (including 80 pleural effusion, 3 ascitic fluid and 4 pericardial effusion), 21 superficial lymph node biopsy, 11 other procedures. 354 (65.7%) patients after EGFR-TKIs failure were performed EGFR mutation testing used by 288 rebiopsy and 66 plasma samples. 181 (51.5%) had T790M mutation. In 66 plasma samples, 29 (36.9%) harbored T790M mutation, 23 (34.8%) with mutation in accordance with before EGFR-TKIs treatment, 14 with wild-type EGFR. In all patients, 341 received further treatment in our hospital; 236 (69.2%) patients treated with chemotherapy, 43 (12.6%) combined TKI controlled local treatment, 42 (12.3%) changed second or third generation TKIs, 33 switched to other treatment. But this part of data still underdone. Conclusion: Rebiopsy is feasible in patients after EGFR-TKIs failure. Rebiopsy could effect on further treatment strategies after especially third generation EGFR-TKI in clinical application. While plasma is also an available surrogate of EGFR mutation testing for patients without suitable lesions for rebiopsy after disease progression.

Keywords: rebiopsy, non-small cell lung cancer, EGFR-TKI, EGFR mutation

P3.02B-105 MUTATIONAL PROFILES OF NON–SMALL-CELL LUNG CANCER PATIENTS RESISTANT TO FIRST-GENERATION EGFR TYROSINE KINASE INHIBITORS USING NEXT GENERATION SEQUENCING
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Background: Patients with advanced non-small-cell lung cancer (NSCLC) harboring sensitive epithelial growth factor receptor (EGFR) mutations invariably develop acquired resistance to EGFR tyrosine kinase inhibitors (TKIs). Although previous research have identified several mechanisms of resistance, the systematic evaluation using next generation sequencing (NGS) to establish the genomic mutation profiles at the time of acquired resistance has not been conducted. Methods: In our single center, we performed NGS of a pre-defined set of 416 cancer-related genes in a cohort of 97 patients with NSCLC harboring TKI-sensitive EGFR mutations at the time of acquired resistance to first-generation EGFR-TKIs between January 2015 to December 2015. Results: In 97 samples we found total 345 gene alterations (mean 3.6 mutations per patient, range 1-10). Fifty-six patients (57.7%) still exhibit EGFR-sensitive mutations as pretreatment, 93 patients (95.9%) exhibit at least one mutation except for previous existed EGFR-sensitive mutations. In all the 97 patients, most frequently mutated genes were TP53 (59.8%), T790M (28.9%), TET2 (11.3%), EGFR amplification (10.3%), PIK3CA (8.2%), BIM (8.2%), KRAS (7.2%), APC (7.2%), RB1 (6.2%), HER2 (6.2%), DNMT3A (6.2%) and MET (5.2%). Conclusion: NGS in this study uncovered many new genetic alterations potentially associated with EGFR TKI resistance and provided information for the further study of drug resistance and corresponding relevant tactics against the challenge of disease progression.

Keywords: non-small cell lung cancer, epithelial growth factor receptor, Tyrosine kinase inhibitors, drug resistance

P3.02B-106 LOCAL EXPERIENCE OF OSMIERTINIB USE; RETROSPECTIVE REVIEW BASED ON PLASMA EGFR USING ddPCR TECHNIQUE
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Background: Osimertinib was approved by FDA in Nov 2016 for treatment of patients with metastatic EGFR-T790M mutation positive NSCLC, as detected by an FDA-approved test (Cobas ® EGFR Mutation Test v2) after EGFR-TKI failure, with an ORR up to 70% and a PFS around 11 months. Methods: We report local experience on EGFR mutations detected by droplet digital polymerase chain reaction (ddPCR) technique on cell free tumor DNA from lung cancer patients, guiding osimertinib therapy after 1st or 2nd generation TKI failure. All patients with plasma EGFR testing done using ddPCR technique from Nov 2015 to Mar 2016 are retrospectively identified and analyzed. Results: 47 patients were tested for EGFR mutations by ddPCR after EGFR-TKI failure. 19 patients had detectable T790M mutant copies of 3.5 - 65887.3 mutant copies/ml plasma (median 61.5). All had previous use of TKI > 6 months (range 171 - 1592 day, median 544). Among the 14 patients who received osimertinib, the median PFS and OS were not reached over a mean follow up of 4.3 months. There was one progressive disease, five stable diseases and eight partial responses as the best treatment response. The number of T790M mutant copies number/ml plasma in the PR group was numerically higher than the SD/PD group (mean 416.5 vs 25.9) but statistically insignificant (p-value 0.15) for difference. Of the limited eight patients having simultaneous tissue biopsy and molecular testing in this cohort, six was concordant with the plasma EGFR result. The two remaining had detectable T790M in plasma EGFR but not in tissue re-biopsy, and, of note, one achieved partial response and one stable disease after osimertinib.

Keywords: ddPCR, plasma EGFR, Tumor heterogeneity, osimertinib

P3.02B-107 EFFICACY OF AFATINIB AND Gefitinib IN LUNG ADENOCARCINOMA WITH EGFR GENE MUTATION AS 2ND OR 3RD LINE TREATMENT
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Background: In Mexico, 85% of patients with lung cancer are diagnosed in an advanced stage. The most effective current treatment is chemotherapy, however only 40% of patients respond to it. A substantial progress is the recognition of several distinct subgroups of Adenocarcinoma that respond differently according to mutations in oncogenes. Patients with EGFR mutation are optimally treated with EGFR tyrosine kinase inhibitors (TKIs). In Mexico, the access to oncologic medication is problematic due to poverty, socio-demographic problems and health access, which impedes treatment initiation with TKIs as first line therapy. We sought to confirm the beneficial effect of TKIs as second or third line therapy on patients with advanced stage
luc cancer adenocarcinoma. Methods: In this retrospective, uncentric study we assigned 41 patients by convenience with lung adenocarcinoma in advanced clinical stage of the disease to receive afatinib or gefitinib as second or third line therapy. The primary endpoint of our trial is to describe progression free survival and global survival outcomes in patients that receive TKIs as second or third line therapy. Secondary end points were time elapsed from the beginning of TKIs to the time of response by RECIST 1.1, and toxicity between the two groups. Conflict of interest: Boehringer Ingelheim donated Afatinib and The National Institute of Respiratory Diseases in Mexico donated Gefitinib. Results: From 120 patients, 41 of them were selected to receive TKIs by convenience. The progression free survival with aafitinib PFS was 11 months and 10 months for gefitinib, with no significant difference in both therapeutic groups (HR 0.79, p=0.173). There is a reduction in 2 years mortality in favor of aafitinib (HR 0.69, p=0.046). There were no significant differences between aafitinib and gefitinib in response rate, also there were no differences by RECIST 1.1. We observed more incidence of mucositis in the group treated with aafitinib (HR 0.58, p=0.006) and metastasis to CNS at diagnosis observed in aafitinib group (p=0.029). Conclusion: There was a reduction in 2 years mortality in favor of aafitinib. With the obtained we can infer that TKIs show similar benefits in second and third line as if given at the beginning, with a good progression free survival, with no significant differences between aafitinib or gefitinib.

Keywords: TKIs treatment, NSCLC 2nd line treatment, EGFR mutation treatment

P3.028-108 ASSESSMENT OF CLINICAL SOLUBILITY OF A CFDNA-BASED ASSAY DETECTING EGFR T790M MUTATION IN EGFR-TKI REFRATORY NSCLC PATIENTS

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Background: Assessment of acquired resistant EGFR mutation T790M in circulating free DNA (cfDNA) in the plasma of EGFR-TKI treated NSCLC patients presents several challenges. Furthermore, the feasibility and required sensitivity of cfDNA-based detection methods in second-line therapy are not well elucidated. Here, we examined the feasibility and required sensitivity of cfDNA-based detection methods in second-line therapy for EGFR as assess the clinical solubility of such data for diagnosis purposes. Methods: cfDNAs were prepared from the plasma samples of 45 NSCLC patients who were confirmed as harboring activating EGFR mutations (exon19 deletions, N = 20; L858R, N = 23; and minor mutations, N = 2). EGFR mutations in cfDNA samples were detected using highly sensitive methods (NGS-utilizing ultra-deep sequencing, droplet digital PCR) and other newly developed assays (BNA-clamped PCR/F-PHFA combined method, and BNA-clamped qPCR) and these results were compared to tissue-based definitive diagnoses. Results: No significant change was observed in amounts of extracted cfDNA among EGFR-TKI-naive (N = 18) and refractory (N = 27) groups. There was a positive significant correlation between the amount of cfDNA and diameter in target regions, suggesting that tumor volume reflects the amount of cfDNA. Significant negative correlation was observed between cfDNA amounts and PFS following EGFR-TKI treatment in the TKI-naive group. The overall percentage agreement between cfDNA and tissue-based analyses ranged from 89 to 100% in major activating mutations and was approximately 85% in T790M. Detected fragment number of each mutation in cfDNA samples by ultra-deep sequencing suggested that it caused the observed difference in the agreement rates between activating mutations and T790M. We confirmed the strong agreement between the high performance of cfDNA assay and that of tissue samples was tested. Next, cfDNA genotyping results were compared to tissue-based definitive diagnosis. In the case of BNA-clamped qPCR, the positive percent agreement was 63% (26/41) in major activating mutations, whereas the negative percent agreement was 100% (45/45). T790M was detected in 46% (12/26) cfDNA samples derived from the EGFR-TKI refractory group. We confirmed re-biopsies in a proportion of enrolled patients and investigated the tissue-plasma results concordance in matched samples. The observed overall percent agreement was 63% in case of T790M and 88% regarding exon19 deletions. Conclusion: Due to heterogeneity or other biological features of drug-treated tumors, the cfDNA assay feasibility of detecting T790M was more limited than that of detecting activating mutations. To assess the T790M status in EGFR-TKI refractory patients, tissue-based assay and cfDNA-based assay should be performed complementarily.

Keywords: EGFR mutation, non-small cell lung cancer, circulating free DNA

P3.028-109 MOLECULAR PROFILING OF EGFR-POSITIVE NSCLC WITH SECONDARY T790M RESISTANCE MUTATION AND TERTIARY TRANSFORMATION INTO SMALL-CELL LUNG CANCER

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Background: In advanced stage NSCLC, activating EGFR mutations are prognostic and predictive factors for treatment with an EGFR-tyrosine kinase inhibitor (TKI). However, invariably, resistance to EGFR-TKI develops. Resistance is primarily driven by T790M mutation present in approximately 50% of EGFR mutation-positive NSCLC at progression. A different mechanism of EGFR-TKI-resistance is transformation into SCLC which has been reported in very rare cases. Methods: Employing Sanger sequencing and targeted next generation sequencing, we performed full histopathological workup and molecular profiling of all minor biopsies obtained during the course of disease. Both molecular and histopathological data were correlated with the clinical course. Results: We report the case of a 70 year old patient, ECOG 1, presenting with dyspnea and fatigue due to a predominantly acinar adenocarcinoma with extensive metastatic disease. Using Sanger sequencing, we detected a del Exon19 EGFR mutation. Based on fulfilled response criteria for EGFR-TKI therapy, erlotinib 150mg was initiated with rapid improvement of dyspnoea and fatigue. After one month, erlotinib was reduced to 100mg due to dermatotoxicity. After 5 weeks, CT showed partial remission. After 4½ months, CT revealed mixed response with resolved pleural effusion but slow progression pulmonary metastases. The brain metastasis present at diagnosis had regressed but a new lesion was detected. Due to ongoing clinical benefit, erlotinib was continued beyond progression. After 7 months, the patient deteriorated clinically (ECOG 2) with CT showing progression of all tumor sites including, FNAC of a progressive mediastinal lymph node was submitted for histopathological and molecular work-up. In parallel one cycle of systemic chemotherapy with carboplatin/gemcitabine was given, and cerebral radiation was delivered. Following detection of a T790M mutation, chemotheraphy was stopped and therapy with osimertinib 80mg (CUP) was started with prompt improvement of the clinical state. CT after 6 weeks confirmed partial remission. However, 10 weeks later, the patient’s condition rapidly deteriorated. CT detected complete remission of brain metastasis but rapid progression of the primary tumour, mediastinal lymphadenopathy, and hepatic metastases. An endobronchial biopsys was performed on minor lung cancer as the underlying cause. EGFR analysis revealed the presence of the original exon19 mutation which had been present in the previous biopsies showing NSCLC histology. Complementing these preliminary results, a full molecular workup using next generation sequencing is currently being performed across all biopsies and will be presented. Conclusion: Integrated analysis of clinical, histopathological and molecular characteristics reveals tumor evolution over time and leads to highly individual therapeutic management benefitting the patient.

Keywords: T790M, SCLC, 3rd generation EGFR-TKI
Abstracts

POSTER SESSION 3 – P3.02B: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/ IMMUNOTHERAPY
EGFR RES - WEDNESDAY, DECEMBER 7, 2016

P3.02B-111 CAN WE AVOID USING CHEMOTHERAPY IN MANAGING ACQUIRED RESISTANCE OF EGFR-MUTATED NSCLC?

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Background: Since the discovery of Non small cell lung cancer with activating mutation of EGFR, most studies have proved that EGFR tyrosine kinase inhibitor to be the treatment of choice with high degree of success and with median response duration of one year. Acquired resistance of EGFR-TKI is inevitable due to various mechanisms including T790M mutation of EGFR, exon 20. Managing acquired resistance of EGFR mutated NSCLC requires special consideration to obtain success particularly to avoid using chemotherapy. Methods: From our own series of advanced NSCLC, 42 patients were indentified as having EGFR mutation for which TKI was used along with other targeted medicine such as Bevacizumab. Of 42 patients treated with multtargeted medicines, 21 cases had proven T790M mutation from re-biopsy while the rest may have T790M or other activating mutations without proven. Those who developed resistance to TKI must have tumor markers rising and tumor site progression and finally have muliple organs progression. Treatment of resistance included: 1) Change to second generation of TKI such as Afatinib 2) Use Anti-PI3K or mTOR-inhibitor such as Torisel 20 mg IV weekly Results: 21 cases of T790M activating mutation came from: 1) 22 cases of classical exon 19 deletion had 5 cases of T790M 2) 7 cases of exon 21 point mutation had 6 cases of T790M 3) 13 cases of various exon 19 mutation had 10 cases of T790M All 21 cases of T790M served the resistance treatment at least 1 year after the discovery T790M. Conclusion: Our results appeared to show: 1) Multiple targeted medicines treatment may avoid the resistance to TKI 2) Those harbored classical exon 19 deletion appeared to have less TKI resistance 3) Those harbored exon 21 EGFR mutation and nonclassical exon 19 mutation appeared to have TKI resistance more (average 1 year 4). We could avoid using chemotherapy in those who developed TKI resistance at least in a short period of time and it will require further study

Keywords: EGFR-TKI resistance

POSTER SESSION 3 – P3.02B: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/ IMMUNOTHERAPY
EGFR RES - WEDNESDAY, DECEMBER 7, 2016

P3.02B-112 FEASIBILITY OF RE-BIOPSY IN PATIENTS WITH NON-SMALL CELL LUNG CANCER AFTER FAILURE OF EPIDERMAL GROWTH FACTOR RECEPTOR TARGETED THERAPY

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Background: After failure of epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI), re-biopsy may be helpful to understand resistance mechanism and guide further treatment decision. However, re-biopsy is still challenging due to several hurdles, such as tissue availability, procedural feasibility, and limited new drugs. The aim of this study was to assess the feasibility of re-biopsy in advanced non-small cell lung cancer (NSCLC) in real-practice. Methods: We retrospectively reviewed the clinical and pathologic data of advanced NSCLC patients who had disease progression after previous EGFR-TKI at single institution between January 2015 and February 2016. Results: Ninety-one patients had disease progression after using EGFR-TKI. Among them, thirty-three patients (36.3%) underwent re-biopsy. re-biopsy was successfully completed for thirty-two patients (97.0%) and only one patient didn't get malignant cell. Three patients (9.1%) experienced a pneumothorax, however only one patient required closed thoracostomy. After re-biopsy, 27 patients were performed EGFR mutation test. Among 21 patients who had active mutation, the initial mutation was again found in 9 cases (42.9%) while the T790M mutation was found in 6 cases (28.6%). In 4 cases the initial EGFR mutation was no longer found. The patients who had re-biopsy were younger (61.2±9.7 years vs. 66.1±10.8 years, p=0.03) and longer response duration (42.9±38.3 vs. 26.5±28.4 days, p=0.022) than the patients who didn't. Conclusion: Re-biopsy in advanced NSCLC is feasible in the real practice especially in younger patient and patients with longer response duration of EGFR-TKI.

Keywords: re-biopsy, EGFR mutation, T790M

POSTER SESSION 3 – P3.02B: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/ IMMUNOTHERAPY
EGFR RES - WEDNESDAY, DECEMBER 7, 2016

P3.02B-113 CLINICAL COURSE OF NSCLC PATIENTS WITH EGFR MUTATION UNDERGOING REBIOLOGY AND OSIMERTINIB THERAPY

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Background: Osimitinib, a third-generation epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI), was approved in May 2016 in Japan. Its administration requires a tumor biopsy to detect the EGFR T790M mutation. AURA and AURA2 studies with 411 patients demonstrated a remarkable clinical outcome with an overall response rate (ORR) of around 65% and progression-free survival (PFS) of 9.7 months. Several authors reported that the detection rate of T790M mutation by tumor biopsy in these patients was approximately 52 to 68%. However, thorough accumulation of data is required to establish the clinical relevance of T790M detection and osimertinib response. Methods: We retrospectively reviewed the clinical courses of NSCLC patients with the EGFR mutation who had undergone rebiotherapy and osimertinib therapy. Results: Eleven patients with the EGFR mutation (exon19del (n=10) and L858R (n=1)) were included. Average age was 67 years old (range 53–79). The following EGFR-TKIs were administered to the 11 patients before rebiotherapy; erlotinib (n=6), afatinib (n=5) and gefitinib (n=2). The patients received rebiotherapy in the 2nd line treatment (n=3), 3rd line (n=2), 5th line (n=2), 6th line (n=2) and 7th line (n=2). Rebiotherapy sites were primary lung tumors (n=8), supraclavicular lymph node (n=1), liver metastasis (n=1) and pleural effusion (1). Among them, 7 patients was detected in four, zero, one, and one, respectively (detection rate: 54.5%). Rebiotherapy was successfully performed in all patients, among whom one required a second attempt. ASPIRE273, another third-generation EGFR-TKI, and osimertinib was administered in one and two patients, respectively. The remaining two patients were to be treated with osimertinib. Both patients who received osimertinib achieved partial response, and their ECOG performance status (PS) was remarkably improved from 4 to 1, and 3 to 1. One of the two patients experienced grade 4 neutopenia; thus, the osimertinib dose was reduced from 80 mg to 40 mg daily. The remaining patient suffered from toxicity however, it was improved after ten-day cessation of medication. Osimertinib was then resumed at 80 mg daily with no severe side effects experienced thereafter. Conclusion: The detection rate of T790M by rebiopsy was consistent with previous reports. Osimertinib was feasible and effective for oncologists and poor PS; however, a prospective study is required to confirm osimertinib’s validity for such patients. In WCLC 2016, we will increase the number of patients who undergo rebiopsy and osimertinib therapy, and we

Keywords: re-biopsy, EGFR mutation, T790M
Background: Both osimertinib and rociletinib were developed to target the EGFR resistance mutation T790M. We retrospectively analyzed data from 790M. Sequist, et al reported clinical benefit with osimertinib in 9 pts previously treated with rociletinib. We conducted a retrospective analysis at 8 institutions of pts treated with rociletinib, who discontinued the drug due to disease progression or intolerable toxicity and subsequently received osimertinib. Methods: We identified pts treated with rociletinib followed by osimertinib, as part of osimertinib development. DCR with osimertinib was assessed using recursive KM method. Results: 65 pts were included in this analysis. Median age at the start of osimertinib was 66 years (43-86) and 71% were female. 28 pts had exon 19 deletions and 16 had L858R. Median duration of therapy on front line EGFR TKI was 18 months (5-54). Median starting dose of rociletinib was 625 mg bid (range 500-1000). The response rate (RR) and disease control rate (DCR) for patients who received rociletinib followed by osimertinib were 38% and 91%; median duration of rociletinib therapy was 6.2 months. 32 (77%) pts discontinued rociletinib for disease progression. 23 (57%) pts received other therapies (1-4) before starting osimertinib. 25 (56%) pts were known to have brain metastases at osimertinib initiation. RR and DCR with osimertinib were 33% and 82%. DCR in the brain was 88%. With a median follow-up of 7.1 months, median duration of osimertinib therapy in all patients was 8 months (95%CI-6.6-6.96; 64% censored). The 1-year overall survival (OS) rate on osimertinib was 70% (95% CI 54-91). In the 32 pts who discontinued rociletinib due to progression, DCR of osimertinib was 75% and median duration of therapy was 7.8 months (4.6-NN). Neither duration of, or response to rociletinib treatment, nor interval between the two drugs was associated with duration of osimertinib or OS after osimertinib using a Cox model adjusted for age and sex. Conclusion: Osimertinib may provide clinical benefit in EGFR mutation positive NSCLC patients previously treated with rociletinib. The clinical activity of osimertinib in these patients may be related to more potent inhibition of T790M mutation or ability to overcome resistance to rociletinib. Reference- 1. Sequist, et al. JAMA Oncology 2016
Keywords: osimertinib, rociletinib, EGFR, 790M
Background: Among patients with EGFR+ inhibits T790M and highly selective, potent cMET inhibitor with clinical activity in patients with on EGFR tyrosine kinase inhibitors (EGFR-TKIs), the most common (50%) S664dialysis and documented cases of drug resistance mutations, which was undetectable due to the intra-tumor heterogeneity.

Keywords: SCLC, transformation, EGFR-TKI, NSCLC

POSTER SESSION 3 – P3.02B: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/IMMUNOTHERAPY
WEDNESDAY, DECEMBER 7, 2016

P3.02B-118 POTENTIAL MECHANISM REVEALED BY TARGETED SEQUENCING FROM LUNG ADENOCARCINOMA PATIENTS WITH PRIMARY RESISTANCE TO EGFR-TKIs
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Background: Epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKIs) has greatly improved the prognosis of lung adenocarcinoma. However, there are still approximately 20% lung adenocarcinoma patients with EGFR sensitive mutations that were primary resistance to EGFR-TKIs treatment. The underlying mechanism is unknown. Methods: This study explored the mechanisms of primary resistance by analyzing T1 paired patients with wild type (PT5) and resistant status (PT5R) (without objective response) and sensitivity (PFS>12months) to EGFR-TKIs by next-generation sequencing (NGS). NGS targeted sequencing was performed on the Illumina X platform for 483 cancer-related genes. EGFR mutation was detected by ARMS initially. Results: Potential primary resistance mechanism was revealed by high frequency mutations unique in EGFR-TKIs resistant group. Among the 11 patients, 54.55% (6/11) carried known resistance mechanism, (2 patients carried MET amplification; 2 patients carried T790M mutation; 1 patient carried HER2 amplification; 1 patient carried PTEN loss). And 45.45% (5/11) carried novel mutations that may lead to drug resistance (2 patients carried TGFBR1 mutation; 1 patient carried TRPM5 fusion gene; both patient both had D1M deletion polymorphism and EGFR uncommon mutation). By analyzing somatic single-nucleotide mutation patterns, we found the frequency of C>G→T/A transitions in primary resistance group was significantly higher than that in sensitive group (0.5 vs 0.39, P=0.012). Conclusion: The mechanism of EGFR-TKIs primary resistance is sporadic. TGFBR1 mutation, TRPM5 fusion gene and EGFR multiple mutations might be associated with EGFR-TKIs primary resistance. Cytosine spontaneous deamination (C→G→A) was positively associated with EGFR-TKIs primary resistance.

Keywords: lung adenocarcinoma, EGFR-TKIs, NGS

POSTER SESSION 3 – P3.02B: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/IMMUNOTHERAPY
WEDNESDAY, DECEMBER 7, 2016

P3.02B-119 YH25448, A HIGHLY SELECTIVE 3RD GENERATION EGFR TKI, EXHIBITS SUPERIOR SURVIVAL OVER OSIMERTINIB IN ANIMAL MODEL WITH BRAIN METASTASES FROM NSCLC
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Background: Currently-available EGFR TKIs are ineffective for the treatment of brain metastases from NSCLC due to limited blood-brain barrier (BBB) penetration. YH25448 is a potent, highly mutant-selective and irreversible 3rd generation EGFR TKI that is able to penetrate the BBB, and targets both the T790M mutation and activating EGFR mutations while sparing wild type (wt). Methods: The biochemical and pharmacological activity of YH25448 were characterized in vitro, and functional cell assays. The animal model with brain metastases from NSCLC was established by implanting luciferase-transfected NCI-H1975 human NSCLC cells carrying the L858R/T790M mutation both subcutaneously and intracranially into nude mice. In this animal model, YH25448 was compared with osimertinib in terms of tumor growth inhibition, survival, weight loss and cold clinical signs. The correlation of PK profiles (plasma, CSF and tumor tissues) with biological activity using inhibition of EGFR phosphorylation (pEGFR) in the tumor tissue was evaluated. Results: YH25448 selectively inhibited EGFR single and double mutant kinase activity with IC50 values of 2 nM for L858R/T790M against 76 nM for wt-EGFR. In the cell proliferation assays, GI50 values were 6 nM, 5 nM, and 711 nM for H1975 cells (L858R/T790M), PC9 cells (del19) and H2073 cells (wt), respectively. In primary cancer cells from patients harboring EGFR mutations, YH25448 showed more potent inhibition of cell growth compared to osimertinib. YH25448 daily dosing at doses ≥25 mg/kg resulted in dose-dependent tumor regression in both subcutaneous and intracranial lesions in mice implanted with H1975 cells. Given its high selectivity against wild type and wide safety margin, there were no changes in the central nervous system. Conclusion: YH25448 is a promising 3rd generation EGFR TKI for the treatment of brain metastases from NSCLC.
in body weight and no abnormal clinical signs. At 10-25 mg/kg, YH25448 achieved more significant, complete tumor growth inhibition and longer overall survival compared to same doses of osimertinib. Dose-dependent inhibition of EGFR expression in tumor tissue by YH25448 treatment was well translated into the in vivo efficacy. Plasma half life of YH25448 was 5.9-6.8 hr and tumor to plasma AUC0–last ratio was 3.0-5.1. YH25448 also showed excellent penetration of the BBB, achieving CSF concentrations exceeding the IC50 value for pEGFR inhibition. Conclusion: The strong in vitro potency and high selectivity of YH25448 for mutant EGFR translated into robust in vivo efficacy. These findings indicate that YH25448 will be able to address the urgent unmet needs for EGFR mutant-positive patients with brain metastases.

Keywords: YH25448, 3rd generation EGFR TKI, brain metastases, BBB, T790M mutation, mouse model

P3.028-120 EGFR T790M, L792F, AND C797S MUTATIONS AS MECHANISMS OF ACQUIRED RESISTANCE TO AFATINIB

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Background: Aftabin is effective for lung cancers harboring common EGFR mutations, Del19 and L858R. We reported that tumors with exon 18 mutations are especially sensitive to afatinib compared with first generation (1G) EGFR-tyrosine kinase inhibitors (TKIs). However, data on the mechanisms of acquired resistance to afatinib are limited. Methods: We established afatinib-resistant clones from Ba/F3 cells transfected with common or exon 18 (G719A and Del18) mutations and PC9 (del E746_A750), HCC4006 (del E746_A750) and 11_18 (L858R) cell lines by chronic exposure to increasing concentrations of afatinib. Separately, afatinib-resistant clones were established from above Ba/F3 cells by exposure to fixed concentrations of afatinib. As a result, all of the three afatinib-resistant cell lines compared with parental cells, whereas L792F was the least resistant to 2G-TKIs, particularly dacomitinib. L858R, G719A, and Del18 clones. Additionally, subsets of Del18 clones acquired only T790M. However, C797S occurred in subsets of PC9/gef as well as xenografts upon EGFR inhibitors were studied. Results: Downstream signals of EGFR in cells were studied using western blot. Growth of PC9/wt and PC9/afa cells (B2 and C4) more significant than that of PC9/gef resistant PC9/afa cells using stepwise increment of afatinib in the medium of wild type PC9 cells. Several clones were selected for further experiments. Bypass track through IGFR may be associated with acquired resistance to afatinib.

Keywords: Acquired resistance, non small cell lung cancer, EGFR tyrosine kinase inhibitor, afatinib

P3.028-121 TARGETING MICR-200C/LIN28B AXIS IN ACQUIRED EGFR-TKI RESISTANCE NON-SMALL CELL LUNG CANCER CELLS HARBORING EMT FEATURES

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Background: MicroRNA (miR)-200 family members (miR-200s) are frequently silenced in advanced cancer and have been implicated in the process of epithelial-to-mesenchymal transition (EMT). We previously reported that miR-200s were silenced through promoter methylation in acquired EGFR-tyrosine kinase inhibitor (TKI) resistant non-small cell lung cancer (NSCLC) cells harboring EMT features. In this study, we examined the functional role of miR-200s in NSCLC cells and investigated the novel approach overcoming acquired EGFR-TKI resistance. Methods: We examined miR-200s expressions and promoter methylation statuses in 34 NSCLC cell lines. Then, we analyzed the altered pathway molecules associated with miR-200c statuses using publicly accessible database. Finally, we examined the antitumor effect targeting the molecules related to miR-200c expression in EGFR-TKI sensitive HCC4006 cells and acquired resistance cell line with EMT features HCC4006-GR cells. Results: In the analysis of NSCLC cell lines, miR-200c expression silenced cell lines showed each promoter methylation. There were significant correlations between miR-200c silencing and several oncogenic pathway alterations, including EM-CF and LIN28B overexpression, in database analysis. In addition, EGFR-wild type cell lines showed lower miR-200c expressions compared to EGFR-mutant cell lines. Introduction of miR-200c by using pre-miR-200c caused LIN28B suppression in HCC4006-GR cells. Interestingly, both introduction of miR-200c and knockdown of LIN28B showed antitumor effect in in vitro and in vivo EMT-cell lines, which was not effective in parental HCC4006. Conclusion: MiR-200c/LIN28B axis plays an important role in acquired resistance to EGFR-TKI and can be a therapeutic target overcoming drug resistance.

Keywords: drug resistance, micro-RNA, NSCLC, EGFR-TKI

Abstracts
Background: Most non-small cell lung cancer (NSCLC) patients responding to gefitinib will eventually develop the resistance. Lysimachia capillipes (LC) capilliposide extracts from LC hemis shows both in vitro and in vivo anti-cancer effects. We investigated whether LC capilliposide combined with gefitinib could overcome the resistance of NSCLC cells to gefitinib, and to identify the involved molecular signaling. Methods: NSCLC cell lines with different sensitivities to gefitinib were studied. Cell proliferation was assessed with MTT assay. Cell apoptosis and cell cycle distribution were measured using cytometry. EGFR-related signaling proteins and Human Phospho-Kinase were analyzed using Western blotting and protein array, respectively. Tumor growth inhibition were evaluated in PC-9-GR xenograft. CCK-8, Ki67 and EGFR were assessed by IHC on tumor tissues. Results: LC capilliposide inhibited cell growth in gefitinib-sensitive and -resistant cells. In gefitinib resistant cell PC-9-GR with T790M mutation, the LC capilliposide combined with gefitinib was potent in cell growth inhibition and apoptosis induction, but no obvious effect on gefitinib-induced G0/G1 arrest. LC capilliposide remarkable blocks the phosphorylation of EGFR downstream signaling molecule AKT, on which LC capilliposide and gefitinib alone had no obvious effect. The Human Phospho-Kinase array further confirmed the enhanced inhibitory effect on the AKT signaling. LC capilliposide treatment also enhanced tumor growth inhibition when combined with gefitinib in PC-9-GR xenografts. Conclusion: LC capilliposide restored the sensitivity to gefitinib in NSCLC cells with acquired gefitinib resistance, suggesting that combination of LC and gefitinib may be a promising therapeutic strategy to overcome gefitinib resistance in NSCLCs with T790M mutation.

Keywords: Lysimachia capillipes, non-small cell lung cancer, Gefitinib resistance, AKT

Conclusion: Although an active agent in clinical practice, osimertinib might not provide an early response for pleural effusion.

Keywords: Osimertinib, pleural effusion, EGFR T790M

Background: Some studies have evaluated the impact of patterns of progression after treatment with tyrosine kinase inhibitors (TKI) in non-small cell lung cancer (NSCLC). We evaluated the patterns of progression and prognosis of NSCLC patients that received TKI. Methods: Using the criteria established by Yang to define models of progression to TKI we did a retrospective analysis. Survival curves were plotted using the Kaplan-Meier method. The Cox proportional hazard model was used for multivariate analysis. Results: Eighty-three NSCLC patients were included: 43 patients with dramatic-progression (51.8%), 26 with gradual-progression (31.3%), and 17 with local-progression (16.9%); demographic and clinical characteristics were similar in all subgroups. There was a significant difference in the median Progression-Free Survival (PFS) among the three groups, for the group with dramatic-progression it was 9.1 months, 16 months for gradual-progression and 11.9 for local-progression (P: 0.044). The overall survival (OS) was different among the three groups, for patients in gradual-progression 56 months, for local-progression 11.9 months and for dramatic-progression 9.1 months (figure A). Additionally 41.7% were treated with afatinib after progression to erlotinib and gefitinib. PFS in all patients was 8.08 months. Patients that present asymptomatic progression have a longer OS compared to those who present symptomatic progression (62 vs 31.3 months; p = 0.048).

Conclusion: Although an active agent in clinical practice, osimertinib might not provide an early response for pleural effusion.

Keywords: Osimertinib, pleural effusion, EGFR T790M
Conclusion: There is a subgroup of patients with NSCLC and EGFR mutations who benefit from erlotinib, and there is a subset of patients with T790M mutation who may benefit from afatinib.

Methods: Between August 2015 and August 2016, 46 patients were enrolled in this retrospective study at the Department of Medical Oncology, Seoul National University Hospital, Seoul, South Korea. The PFS and OS of these patients were evaluated.

Results: The median follow-up period was 23 months (range, 1-45 months). The median PFS was 9.2 months (95% CI: 4.7-13.7 months). The median OS was 18.8 months (95% CI: 8.8-28.8 months). The median progression-free survival (PFS) in patients with T790M mutation was 28.1 months (95% CI: 16.5-39.7 months), and the median OS was 31.2 months (95% CI: 23.7-38.8 months).

Conclusion: The results of this study suggest that erlotinib is a valid treatment option for patients with EGFR T790M mutation-positive NSCLC.
Abstracts

the safety of dose level 1, we enrolled additional patients at this dose level and one of the total of six patients treated at this dose level experienced DLTs (AST and ALT elevation, each of grade 3). Exposure of SASP following oral administration was markedly among individuals according to ABCG2 and NAT2 genotypes as previously reported. Conclusion: SASP 500 mg TID was the recommended dose when administered with CDDP plus PEM.

Keywords: Cancer stem cell, non-small cell lung cancer, chemotherapy, Salazosulfapyridine

POSTER SESSION 3 - P3.02C: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/ IMMUNOTHERAPY TARGETED THERAPY – WEDNESDAY, DECEMBER 7, 2016

P3.02C-002 MANNOSYLATED POLY (PROPYLENE IMINE) DENDRIMER MEDIATED LUNG DELIVERY OF ANTIMICROBIC

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Background: Tumors originating in lung tissues or in the bronchi invade adjacent tissue and cause infiltration beyond the lung. Lung macrophages express mannose-specific endocytosis receptor that might binds or internalize mannose terminated dendrimer. Therefore, it is hypothesized that incorporation of antibiotic drug into mannose anchored dendrimer will transport the drug effectively to the tumor cells via receptor mediated endocytosis. Dendrimer are easy to synthesis and better stability, Nanoscopic size range, High drug loading propensity, Dose reduction possible, Number endocytosis. Dendrimer are easy to synthesis and better stability, Nanoscopic size were characterized by Transmission Electron Microscopy (TEM), drug loading efficiency, In-vitro drug release and stability studies. The ex-vivo studies constituted Hemolytic toxicity study and Cell cytotoxic study by MTT Cytotoxicity Assay on A-549 (Lung adenocarcinoma epithelial) cell line. The in-vivo studies were performed on albino rats and Pharmacokinetic parameters were studied, also Biodistribution Studies were done to access gemcitabine level attained in different organs. Results: Thus Mannosylated PPI dendrimers showed high gemcitabine loading, sustained release and excellent biocompatibility as evident by low hemolytic toxicity. MTT assay suggested high cytotoxicity of GmcH-MPPI against A549 cancer cell lines. The Presence of ligand on dendrimer molecule, elevated receptor mediated binding or internalization in AM. The developed ligand conjugated dendritic system targeted higher concentration of GmcH to lung than the free drug. Conclusion: Thus, we concluded that GmcH loaded mannosylated PPI dendrimer system could have higher potential to target anticancer drug to lungs for effective chemotherapy of lung tumor.

Keywords: Dendrimer, Lungs, Gemcetabine

POSTER SESSION 3 - P3.02C: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/ IMMUNOTHERAPY TARGETED THERAPY – WEDNESDAY, DECEMBER 7, 2016

P3.02C-003 TAX-TORC: THE NOVEL COMBINATION OF WEEKLY PACLITAXEL AND THE DUAL MTORC1/2 INHIBITOR AZD2014 FOR THE TREATMENT OF SQUMOUS NSCLC

Matthew Krebs1, James Spencer2, Nicola Steele1, Denis Talbot3, Michael Brada4, Richard Wilson5, Robert Jones6, Bristi Basu7, Joanna Dawes7, Mona Parmar5, Beth Purchase4, Alison Turner6, Emma Hall7, Bristi Basu9, Holly Tovey7, Udai Banerji1, Timothy Yap7
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Background: The dual mTORC1/2 inhibitor AZD2014 has multiple effects on cell growth, apoptosis, angiogenesis and metabolism in cancer cells. AZD2014 increases the efficacy of paclitaxel in preclinical models, including patient derived xenografts. These data and clinical responses in the dose escalation arm of the TAX-TORC study led to an expansion cohort of 40 patients with squamous non-small cell lung cancer (SCLC). Methods: Forty-two patients treated (27% stage IIIB/IV, 73% stage IV). AZD2014 was dosed once weekly at 80mg/m2, 5 weeks out of 7. AZD2014 was dosed BD, 3 days per week starting with the paclitaxel dosing. The cohort was started at a starting AZD2014 BD. Results: Thirty-two patients have been treated, 24 male/8 female with median age 68 years. The median number of previous treatments was 1 with 6/32 (19%) having received a prior taxane (docetaxel or paclitaxel). Analysis of data from the first 17 patients, by the safety review committee, showed that fatigue, skin rash and diarrhoea were the most common toxicities in 50%, 47% and 41% patients respectively. The majority of toxicities were CTCAE grades 1 or 2 (112/131, 91%) and reversible with AZD2014 interruption or reduction. However, there were 9 grade 3 and 4 toxicities and 2 incidences of grade 5 respiratory infection. There were 2/17 (12%) responses though patients often stopped early due to toxicity. Following the safety review, the dose of AZD2014 was reduced to 25mg BD which is a pharmacodynamically active dose associated with fewer toxicities. Fifteen additional patients have subsequently been treated at this lower dose. Their most common toxicities were anaemia, anorexia and fatigue in 47%, 47% and 41% patients respectively. There were no grade 5 events and only 8/78 (10%) grade 3 or 4 toxicities. The response rate in this cohort is 5/15 (33%) and recruitment is ongoing. Archival samples and circulating free DNA at baseline are being assessed with targeted next generation sequencing to explore putative predictive biomarkers for response and resistance. Conclusion: We have established a tolerable dose and schedule for the combination of weekly paclitaxel and AZD2014. The promising response rate of 33% in previously treated nsQNSCLC patients warrants further investigation. The study is supported by AstraZeneca, Cancer Research UK, Experimental Cancer Medicine Centre and NHS Biomedical Research Centre Initiatives.

Keywords: squamous, paclitaxel, Phase 1, mTORC
for the treatment of NSCLC. SBI0206965 may be a promising agent for the treatment of NSCLC by modulating autophagy and apoptosis pathways. Furthermore, the combination of SBI0206965 with classical chemotherapy agents represents a promising therapeutic strategy that warrants further clinical evaluation in NSCLC.

Keywords: Autophagy, SBI0206965, UKI, NSCLC

P3.02C-005 MET EXON 14 SKIPPING IN QUINTUPLE-NEGATIVE (EGFR-/KRAS-/ALK-/ROS1-/RET-) LUNG ADENOCARCINOMA
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Background: MET exon 14 (METex14) skipping has been reported as a potentially targetable driver mutation in lung adenocarcinoma. We aimed to evaluate the prevalence and clinicopathologic characteristics of lung adenocarcinoma harboring METex14 skipping in patients with lung adenocarcinoma in which targetable genomic alterations are not available. Methods: We screened 795 patients with lung adenocarcinoma and 45 patients with quintuple-negative (EGFR-/KRAS-/ALK-/ROS1-/RET-) lung adenocarcinomas were finally included to identify the patients harboring METex14 skipping by using RT-PCR with probes overlapping an exon 13–15 junction. In addition, we summarized recent articles reported about METex14 skipping in lung cancer. Results: Based on the present study, seventeen (37.8%) had tumors harboring METex14 skipping alterations. Diverse genomic sequence variants causing METex14 skipping were identified. The median age of the METex14 skipping-positive patients was 73 years (range, 55–81 years), 8 patients (47.1%) were female, and 7 (41.2%) had never smoked. The most frequent cause of METex14 skipping was acinar followed by the solid type. The MET immunohistochemistry test for METex14 skipping demonstrated 100% (95% CI, 95.6–100) sensitivity and 70.4% (95% CI, 51.5–84.2) specificity. In an immunohistochemistry test for MET, ex14 skipping was identified in 14.6% (45/309) of the patients. The prevalences of METex14 skipping were 12.9% (20/155) in sarcomatoid carcinoma, 3.9% (11/282) in adenosquamous carcinoma, 2.6% (398/15050) in adenocarcinoma, 2.1% (26/1262) in squamous cell carcinoma, and 0.8% (2/243) in large cell carcinoma, respectively. Conclusion: The prevalence of METex14 skipping was relatively high in patients with quintuple-negative (EGFR-/KRAS-/ALK-/ROS1-/RET-) lung adenocarcinomas. Lung adenocarcinomas harboring METex14 skipping were associated with old age, acinar or solid histology, and MET protein overexpression. Identification of subpopulation harboring METex14 skipping can be an important step toward developing targeted therapies for patients with lung cancer.

Keywords: clinicopathologic feature, Adenocarcinoma, lung cancer, MET exon 14 skipping

P3.02C-006 EGFR AND HER3 INHIBITION - A NOVEL THERAPY FOR INVASIVE MUCINOUS NON-SMALL CELL LUNG CANCER HARBORING AN NRG1 FUSION GENE
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Background: Invasive mucinous adenocarcinoma of the lung (IMA) accounts for 2 to 10% of all lung adenocarcinomas and usually presents as a multifocal and unrespectable disease for which no effective treatment exists. Recently, rearrangements of the HER3 ligand gene NRG1 have been identified in IMA such as NRG1-SLC3A2 and NRG1-CD74 leading to activation of HER3 and PI3K-AKT signaling pathways. Therefore, IMA harboring NRG1 fusion genes may serve as a biologically attractive target for HER3-targeted therapies. Methods: Study NCT01482377 is a phase Ib study analyzing the safety and preliminary efficacy of lumretuzumab, a monoclonal anti-HER3 antibody, in combination with erlotinib in patients with HER3 protein-positive tumors. Lumretuzumab IV was given every 2 weeks at 800 mg and erlotinib was given at standard dose of 150 mg/d. A pretreatment tumor biopsy was mandated for the assessment of membranous HER3 protein by IHC. NRG1 fusion genes were identified by RT-PCR and sequencing. Tumor assessments were performed by CT scans every 8 weeks. Therapy was given until progressive disease or unacceptable toxicity. Here we describe the clinical course of two patients with IMA harboring a SL3A2-NRG1 fusion gene treated within this study. Results: Patient 1 is a 55-year-old Asian female who was diagnosed in 2011. Previous lines of therapy included gemcitabine and cisplatin, erlotinib, pemetrexed, docetaxel and irinotecan and cisplatin. After enrolling into the study the first CT scan showed a decrease of 16% of the target lesion qualifying for stable disease per RECIST 1.1. At the following tumor assessment progressive disease was documented resulting in a disease stabilization of 16.4 weeks. Patient 2 is a 42-year-old Asian female who was diagnosed in 2013. Previous lines of therapy included pemetrexed and cisplatin, erlotinib, docetaxel, vinorelbine, and gemcitabine and cisplatin. After enrolling into the study, the patient showed stable disease as a best overall RECIST response that lasted 16.3 weeks. Both patients experienced mild to moderate rash and diarrhea (grade 1 & 2). No ≥ grade 3 adverse events were observed. Conclusion: This is the first report of a novel targeted therapy approach in IMA patients harboring NRG1 gene rearrangements. We identified a biological entity that is generally considered to be extremely difficult to treat. The combination of lumretuzumab and erlotinib was well tolerated and showed signs of tumor shrinkage in a heavily pretreated IMA patient. Further studies are warranted to elucidate the clinical relevance of HER3-targeted therapy in IMA patients with NRG1 fusion genes.

Keywords: NRG1, lung cancer, HER3, gene fusion

P3.02C-007 ASSESSMENT OF DIANHYDROGALACTITOL IN THE TREATMENT OF RELAPSED OR REFRACTORY NON-SMALL CELL LUNG CANCER
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Background: Non-small cell lung cancer (NSCLC) is treated with surgery and chemotherapy with either tyrosine kinase inhibitors (TKIs) or platinum-based regimens, but drug resistance is frequent and long-term prognosis poor. Dihydrogalactitol (VAL-083) is a bifunctional alkyating agent with proven activity against NSCLC in clinical studies. VAL-083 has demonstrated superior activity to cisplatin in both in vitro and in vivo NSCLC models, including TKI-resistant NSCLC, and circumvents cisplatin-resistance in ovarian cancer cells. VAL-083 is approved for the treatment of lung cancer in China; however, clinical adoption is limited by lack of modern data related to mechanism-of-action and utility in the context of standard-of-care platinum-based chemotherapy. Here we aimed to investigate in vivo i) the distinct mechanism-of-action of VAL-083, ii) VAL-083 cytotoxicity in a panel of NSCLC cell-lines with varying p53 status, and iii) the combination of VAL-083 and cisplatin or oxaplatin. Methods: VAL-083 cytotoxicity was investigated in a panel of 11 human NSCLC cell-lines: 3 wild-type (H460, A549, H226), 6 mutant (H1975, SKL122, H157, H1792, H23) and 2 null (HBB3, H1792) for p53. Cell-cycle and DNA damage was investigated by propidium iodide and rhodamine fluorescent stains in synchronized cell lines H1975 and H1792, A549. Cytotoxicity was determined by MTT assay. Combination potential for VAL-083 with cisplatin or oxaplatin was investigated in H460, A549, H1975 (TK1-resistant) by determining superadditivity and synergy using the combination index (CI) criteria. Results: VAL-083 treatment caused persistent S/G2 cell-cycle arrest and cell-death. Furthermore, one-hour pulse treatment led to phosphorylation of DNA double-strand break sensors ATM, single-strand DNA-binding Replication Protein A (RPAP32), and histone variant H2A.X, suggesting activation of the homologous repair pathway. S/G2 phase cell-cycle arrest and increased H2A.X in cancer cells persisted >72 hours after treatment, indicating irreversible DNA lesions. Importantly, VAL-083 was active against all cell-lines tested, irrespective of their p53
status, suggesting a mechanism-of-action that differs from other alkylating agents, including cisplatin. When combined with either cisplatin or oxaliplatin in vitro, VAL-083 demonstrated significant superadditivity (p<0.05) and synergism (CI<1) for both combinations in all NSCLC cell lines. This strongly suggests non-overlapping modes-of-action between the platinum drugs and VAL-083 and demonstrates synergism in TK1-resistant cell lines. Conclusion: This preclinical data strongly suggests VAL-083 as a potential treatment for platinum and TK1-resistant NSCLC. An open-label post-market clinical trial in China is investigating the activity of VAL-083 in relapsed/refractory NSCLC. Results will provide guidance to physicians under the context of VAL-083’s current approval in China, as well as serve as proof-of-concept for expanded development worldwide.

Keywords: NSCLC, alkylating agent, drug resistance, dianhydrogalactitol

P3.02C-008 A MET INHIBITOR IN THE TREATMENT OF METASTATIC NON SMALL CELL LUNG CANCER WITH MET AMPLIFICATION
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Abstract: Amplification of the mesenchymal-epithelial transition factor (MET) gene plays a vital role in non-small cell lung cancer (NSCLC). The anti-MET therapeutic strategies are still unclear in epidermal growth factor receptor (EGFR) mutant patients and EGFR-naive patients. Aims of our study are to discuss role of MET amplification in Chinese NSCLC patients, and evaluate the antitumor activity of crizotinib (MET inhibitor) in Chinese NSCLC patients with MET gene amplification. Methods: From Jun 2015 to Jan 2016, we detected 11 metastatic NSCLC patients with MET amplification by fluorescence in situ hybridization (FISH). MET amplification was defined as gene focal amplification or high polysomy (at least 15% cells with ≥5 copy numbers). Results: The frequency of MET de novo amplification was 5.6% (6/111), and that of concomitant MET acquired amplification and EGFR mutation was 4.5% (5/111) respectively. 4 of 6 patients with MET de novo amplification received crizotinib, 2 patients had partial response (PR), 1 patient had stable disease (SD), 1 patient died due to heart disease. Response rate (RR) of crizotinib was 50%/2(4/8). Encouraging response was observed in one case, a CT scan performed 31 days after starting crizotinib revealed 42.2% decrease in tumor measurement, until now, a 7-month CT revealed 60.0% decrease. 3 of 5 patients with concomitant MET acquired amplification and EGFR mutation received combined therapy of EGFR-tyrosine kinase inhibitors (TKIs) and crizotinib. Partial response was observed in one case with combined therapy, a 2-month CT revealed 31.0% decrease in tumor measurement. Conclusion: According to our study, patients with MET amplification benefited from crizotinib, and RR was inspiring. Patients with concomitant MET acquired amplification and EGFR mutation need combined targeted therapy.

Keywords: metastatic non small cell lung cancer, EGFR, MET inhibitor

P3.02C-010 RESISTANCE MECHANISMS TO PI3K-MTOR INHIBITION IN NSCLC
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Abstract: Background: Non-small cell lung cancer (NSCLC) is a leading cause of cancer mortality globally, having a 5-year survival rate of less than 15%. PI3K-mTOR signalling has been implicated in various hallmarks of cancer and this pathway is often dysregulated in NSCLC. Efforts to therapeutically target the PI3K-mTOR pathway have been hindered by emerging drug resistance. In this study we investigated drug resistance mechanisms associated with the inhibition of PI3K-mTOR pathway, with an emphasis on the mechanisms of acquired resistance, following chronic exposure to a Phase II PI3K-mTOR inhibitor (GDC-0980). Additionally, short term exposure of BEZ235 (another phase II PI3K-mTOR inhibitor) and IBL-301 (a novel PIM/PI3K/mTOR inhibitor) were investigated for their effects on cell viability/proliferation and downstream signalling pathways. Methods: Alterations to the mRNA expression profile of GDC-0980 acquired resistant H1975 cells versus matched parent cells were examined using an 84-gene IL-6/STAT3 signalling specific profiler array. Subsequently, selected genes were validated by qPCR. The effectiveness of BEZ235 and IBL-301 on cell viability of two lung cancer cell lines (H1975 and H1838) following 72 hour treatment were investigated by Cell Titre Blue. pAkt and p4E-BP1 expression were examined by Western blot analysis, following treatment with BEZ235 and IBL-301 at 3, 6 and 24 hours. Results: Thirty candidate gene alterations were identified from the array profile and 6 candidate genes were chosen for validation by qPCR (n=3). The AP2 transcription factor and pro-metabolic regulator mTOR and the anti-apoptotic protein BCL-2 were downregulated (both p<0.01) in GDC-0980 resistant cells. Expression of these targets was upregulated by BEZ235 and IBL-301 following 72 hour treatment by Western blot analyses. pAkt and p4E-BP1 expression were examined by Western blot analyses, following treatment with BEZ235 and IBL-301 at 3, 6 and 24 hours. Results: Thirty candidate gene alterations were identified from the array profile and six candidate genes were chosen for validation by qPCR (n=3). The AP2 transcription factor and pro-metabolic regulator mTOR and the anti-apoptotic protein BCL-2 were upregulated in GDC-0980 resistant cells (p<0.05 and p<0.01). Similarly, FN-α and its receptor co-stimulatory molecule CD40 were increased (p<0.05 and p<0.01). Furthermore, the cell cycle inhibitor, CDKN1 and JAK-signalling blocker, SOCS1 were downregulated (both p<0.01) in GDC-0980 resistant cells. BEZ235 and IBL-301 had a dose-dependent effect on the viability of NSCLC cell lines with high IκBα, values of 9.42nm/l and 13.65nm/l in H1975 cells and 103.35nm/l and 159.27nm/l in H1838 cells. Treatments of 250nm/BEZ235 or IBL-301 inhibited pAkt at all time points in the lung cancer cell lines. BEZ235 blocked translation repression protein (p4E-BP1) across all 3 cell lines and time points while IBL-301 treatment resulted in a reduction in p4E-BP1 at 24 hours.
Conclusion: This study highlights a number of genes involved in IL-6/STAT3 signalling that may contribute to PI3K-mTOR inhibitor resistance. BEZ235 and IBL-301 both decrease cell viability and inhibit PI3K pathway signalling and cap-dependent translation in NSCLC cell lines that warrant further investigation.

Keywords: PI3K-mTOR, IL-6/STAT3 signalling, resistance, NSCLC

P3.02C-011 A PHASE 1B OPEN-LABEL STUDY OF PEGPH20 COMBINED WITH PEMBROLIZUMAB IN PATIENTS WITH SELECTED HYALURONAN-HIGH SOLID TUMORS
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Background: Hyaluronan (HA) is a megadalton polysaccharide found in the tumor microenvironment (TME). HA accumulation in the TME increases tumor interstitial pressure, which promotes vascular collapse and limits access of chemotherapy and immune cells to tumor sites. In animal models, HA-High tumors exhibit increased growth and metastasis, treatment resistance, and reduced survival. PEGPH20 is a pegylated recombinant human hyaluronidase that enzymatically degrades tumor HA. Pembrolizumab (PEM) is a humanized monoclonal antibody targeting PD-1 and demonstrating tolerability and activity in patients with non-small cell lung cancer (NSCLC). This study evaluates the safety and activity of PEGPH20 plus PEM in patients with HA-High tumors. Methods: This is a Phase 1b study comprising a dose escalation portion (up to 30 patients without regard to HA status) followed by a cohort expansion portion in up to 31 patients with HA-High tumors, determined using a companion diagnostic assay developed in collaboration with Ventana Medical Systems. Eligible patients are ≥18 years, ECOG PS 0-1, with either relapsed/refractory stage IIIb/IV NSCLC who failed ≥2 previous platinum-based chemotherapy regimens or relapsed/refractory locally advanced or metastatic gastric adenocarcinoma who failed ≥2 previous chemotherapy regimens. Patients with NSCLC known to be epidermal growth factor receptor (EGFR)- or anaplastic lymphoma kinase (ALK)-positive must have received an EGFR inhibitor or ALK inhibitor, respectively. PEGPH20 (1.6, 2.2, 2.6, 3.0, 4.0 mg/kg) is administered intravenously (IV) over 10 minutes on days 1, 8, and 15 of each 21-day cycle followed by PEM 2 mg/kg IV on day 1, 4 to 6 hours after PEGPH20 is completed. Piroxicam will be given prophylactically for possible musculoskeletal events. Prophylactic proton pump inhibitors will be given to all patients. The primary endpoint for the dose escalation portion is the recommended Phase 2 dose for PEGPH20 in combination with PEM. In the cohort expansion portion, the primary endpoint is objective response rate per RECIST v1.1. Secondary endpoints are duration of response, disease control rate, progression-free survival per RECIST and immune-related response criteria, pharmacokinetics, and adverse events. Exploratory endpoints in patients with HA-High NSCLC include HA levels in plasma and tumor tissue and imaging parameters of tumor blood flow (dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI)) and tumor metabolic activity (position emission tomography/computed tomography (PET/CT) scans). ClinicalTrials.gov Identifier: NCT02565348. Results: Section not applicable

Conclusion: Section not applicable

Keywords: hyaluronan, PD-1, PEGPH20, pembrolizumab

P3.02C-012 APATINIB, A NEW SMALL MOLECULAR VEGFR2 INHIBITOR, SUPPRESSES THE ACTIVITY OF LUNG CANCER STEM CELLS
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Background: Cancer stem cells (CSCs) represent a small fraction of stem-like cells in the cancer that are characterized by their ability for self-renewal, proliferation, resistance to chemotherapy and radiation therapy, multipotent capability, and expression of stem cell markers. CSCs play essential role in cancer progression, chemoresistance, recurrence, and metastasis. Apatinib is a new small molecular VEGFR2 inhibitor which has been approved for the treatment of advanced or metastatic, chemo-refractory gastric cancer patients in China, and a phase II study evaluating its efficacy in patients with advanced NSCLC after second-line chemotherapy is currently ongoing. To date, however, no information is available regarding the action of Apatinib on CSCs. Therefore, the present study aimed to investigate the inhibitory effects of Apatinib on lung CSCs.

Methods: Tumorsphere formation assay via serum-free medium (SFM) culturing was utilized to isolate and enrich lung CSCs from human lung cancer cell lines A549 and H1299. Protein and mRNA expression of lung CSCs markers, including CD133, CD44, ALDH1, Nanog, Sox2 and Oct4, was determined by Western blotting and qR-PCR in sphere-forming A549 and H1299 cells. The number of CD133+ cells was measured by Flow cytometry assay. Following the treatment of sphere-forming A549 and H1299 cells with Apatinib at various concentrations (0-10 μM), the inhibitory effects of Apatinib on lung CSCs were determined by tumorsphere formation, CSCs markers’ expression, number of CSCs, cell proliferation, apoptosis, activation of CSCs regulating signal pathways including Wnt/β-catenin and Sonic Hedgehog pathways, as well as the expression of VEGFR2 and ABC drug resistance proteins. Results: We revealed that sphere-forming A549 and H1299 cells in SFM culturing exhibited lung CSCs properties. Apatinib suppressed the sphere formation capacity of these cells in a concentration-dependent manner. The expression levels of lung CSCs markers and the number of CD133+ cells were significantly downregulated by Apatinib. Our results further showed that Apatinib significantly inhibited the activation of Wnt/β-catenin and Sonic Hedgehog pathways, inhibited cell proliferation, and induced apoptosis in sphere-forming cells. Moreover, we demonstrated that Apatinib markedly reduced the expression levels of VEGFR2, as well as drug resistance proteins p-pg and ABC02. Conclusion: Taken together, these data suggest for the first time the inhibitory effects of Apatinib on lung CSCs. Findings from this study would provide a solid basis for the application of Apatinib in chemo-refractory lung cancer patients.

Keywords: VEGFR2 inhibitor, Lung cancer stem cells, chemoresistance, Apatinib

P3.02C-013 COMBINATION THERAPY OF ONCOLYTIC HERPES SIMPLEX VIRUS TYPE 1 WITH ERLOTINIB IN A HUMAN LUNG CANCER XENOGRAFT MODEL
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Background: Despite the development of a number of new targeted therapies, lung cancer remains the leading cause of cancer-related death worldwide. The use of oncolytic herpes simplex virus type 1 (HSV-1) has been shown to be an effective therapeutic approach for a variety of cancers in preclinical models. A third generation oncolytic HSV-1, G47Δ, is currently used in multiple clinical trials in Japan. Methods: In this study, we evaluated the efficacy and safety of G47Δ when used in combination with erlotinib, an epidermal growth factor receptor tyrosine kinase inhibitor, in lung cancer xenograft models in mice. Human lung cancer cell line A549 subcutaneous tumor-bearing mice were treated with G47Δ and erlotinib, each alone or in combination, and effects on tumor volume were determined. The toxicity was evaluated by body weight changes. Results: In this subcutaneous mouse model, combination therapy resulted in the inhibition of tumor growth without toxicity to a greater extent than that using each agent alone. Conclusion: These findings suggest that combination therapy of G47Δ and erlotinib may be a new treatment strategy against human lung cancer.

Keywords: Oncolytic virus therapy, HSV, Erlotinib, EGFR-TKI

P3.02C-014 PATIENTS WITH RECURRENCE AFTER RESECTION OF LUNG CANCER ARE GOOD CANDIDATES FOR THE BEYOND OVER PROGRESSIVE DISEASE APPLICATION OF BEVACIZUMAB

Abstracts

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Background: The benefit of the continuation of bevacizumab (BEV) beyond over progression disease (PD) in patients with non-squamous cell lung cancer (NSCLC) has not been clarified yet. We present our experience of chemotherapy with BEV continuation beyond PD in patients with recurrent NSCLC after surgery. Methods: They were consisted of 19 patients. There were 10 males and 9 females, and their age at surgery was 69±10 (41-85 years) old. Lobectomy was done in 18 patients, and segmentectomy in 1. Pathological stage was IAs in 5, IBs in 3, IIBs in 3, IIIAs in 5, IIIBs in 1, and IV in 2. Recurrence was observed at 630±460 days after surgery. Sixteen patients among them had been received some chemotherapy protocols before usage of BEV for 507±448 days. Performance status before treatment was grade 0 in 11 patients, 1 in 7, and 2 in 1. Chemotherapy was performed in the 1st line. We decided to continue BEV beyond PD in these patients. Results: The average number of protocols with BEV was 3±1(1.5). BEV was used for 173±414 days. Side effects (≥ grade 2) due to BEV were hypertension in 6 patients, proteinuria in 4, and hemoptysis in 1. Seven patients were died of cancer, and 1 of COPD worsening. Five-year survival rate after surgery, after recurrence, and after initiation of BEV was 81.2%, 45.0%, and 31.2%, and median survival time was 2384 days, 1661 days, and 1105 days, respectively. Conclusion: The majority of patients with operable NSCLC have good performance status. Moreover, we can detect their recurrence in the early periods at most before the symptoms appear, because of the regular examinations. Therefore, these patients are at an advantage that they can receive more chemotherapy protocols. In these selected patients, their prognosis may be prolonged by the continuation of BEV beyond over PD.

Keywords: beyond over PD, bevacizumab

P3.02C-015 PHASE II TRIAL OF S-1/CISPLATIN COMBINED WITH BEVACIZUMAB FOR ADVANCED NON-SQUAMOUS NON-SMALL CELL LUNG CANCER: TC0G LC12-022
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Background: S-1 plus cisplatin is a standard chemotherapy regimen for advanced non-small cell lung cancer (NSCLC). The addition of bevacizumab significantly improved overall survival (OS) in patients with advanced non-squamous (non-SQ) NSCLC who received carboplatin plus paclitaxel but failed to show an OS advantage in patients with advanced non-SQ NSCLC. Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0-1, age 20-74 years, and measurable lesions were treated with a 3-week cycle of 5-140 mg/m² twice a day on days 1-14, cisplatin 60 mg/m² on day 8, and bevacizumab 15 mg/kg on day 8, for 4-6 cycles. Patients without progressive disease received maintenance bevacizumab 15 mg/kg twice a week and 5-140 mg/m² twice a day every other day. The primary endpoint was progression-free survival (PFS). Secondary endpoints were objective response rate (ORR), OS, toxicity profile, and QOL. Results: From June 2013 to January 2015, 39 evaluable patients were enrolled from 8 institutions: 10 women and 29 men; median age 65 years (range, 38-70 years); epidermal growth factor receptor positive/anaplastic lymphoma kinase positive: two patients/two patients; performance status 0/12/217; stage IIIB/IV: recurrence: 1/35/3, adenocarcinoma/other: 35/1/3. Thirty one patients (80%) completed 4 cycles of induction chemotherapy, and 23 patients (59%) were started on maintenance chemotherapy. Median PFS, OS, and ORR were 7.3 months (95% confidence interval (CI): 5.9-8.7), 21.4 months (95% CI: 14.7–not reached), and 64%, respectively. The worst hematologic and non-hematologic adverse events were as follows (%): grade 3/4 leukopenia: 13/0; neutropenia: 18/5; thrombocytopenia: 0/0; anemia: 0/0; neutropenic fever: 3/0; and hypertension: 28/0; diarrhea: 3/0. QOL data will be presented at the meeting. Conclusion: S-1 plus cisplatin in combination with bevacizumab met the primary endpoint in patients with advanced non-SQ NSCLC in the present trial. Additionally, the response rate is anticipated to be high, and the regimen was well tolerated. Clinical trial information: UMIN000009476

Keywords: bevacizumab, Non-squamous non-small cell lung cancer, TS-1
and apoptosis were measured with Annexin V staining by flow cytometry. Statistical analysis was performed by GraphPad Prism (version 6). Results: In small cell lung cancer cells, following 24h incubation, combinations of docetaxel and meloxicam, docetaxel and ibuprofen, docetaxel and indomethacin, showed increased apoptosis when compared to docetaxel alone (p<0.0001). In non-small cell lung cancer cells, the 24h incubation was not enough to induce satisfactory apoptosis, but following 48h incubation, docetaxel plus indomethacin showed more cytotoxicity when compared to docetaxel alone (p<0.0001). Conclusion: Depending on the drug, the synergistic effect of COX-2 inhibitors plus chemotherapy agents has been demonstrated in lung cancer. Our suggestion is that COX-2 inhibitors could be used as additive and maintenance treatment in combination to antineoplastic agents in lung cancer patients.

Keywords: in vitro, lung cancer, COX-2 inhibitors

POSTER SESSION 3 – P3.02C: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/IMMUNOTHERAPY
TARGETED THERAPY – WEDNESDAY, DECEMBER 7, 2016

P3.02C-017 ‘2ND LINE’ RET-INHIBITION IN A FEMALE PATIENT WITH NON-KIF5B RET-TRANSLLOCATION
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Background: RET rearrangement in unselected non-small cell lung cancer (NSCLC) is expected in 1-2%, most common in adenocarcinomas, young, never or former light smoker. Multikinase Inhibitors such as cabozantinib or vandetanib have shown activity against RET rearranged lung cancer in vitro and in vivo. ORR is about 40% and median duration of response about 8 month with cabozantinib. Progression after RET-inhibition warrants further strategies. 2nd line RET-inhibition might overcome resistance. Methods: We report about a 77 year old female patient with primary diagnosis of adenocarcinoma of the lung with malignant pleural effusion, stage IV, in 08/13. Results: EGF-R mutation, ALK- and ROS1-translocation were negative at initial diagnosis. 111 line therapy with erlotinib and pazopanib resulted in stable disease and clinical deterioration. A VATS was performed with partial resolution of pleural effusion. 211 line therapy with pemetrexed for 16 months resulted in a clinical benefit (cough and dyspnoe, ECOG raised from 2 to 0). In 07/15 CT scan revealed a dissiminated progression with multiple intrapulmonary nodules, clinically corresponding with cough and dyspnoe again. Molecular diagnostic for c-MET, BRAF, KRAS, HER2, PD-L1 revealed new no targets, but a positive RET-FISH testing from initial biopsy. From 10/15 to 03/16 the patient had a good clinical benefit from cabozantinib (multikinase inhibition, including RET). Clinical symptoms resolved in 10 days and ECOG raised from 1 to 0. In 03/16 new hepatic and lymphonodular lesions occurred and the patient suffered again from former clinical symptoms. One cycle gemcitabine was without any benefit. In 04/16 we started with docetaxel 35mg/m2 on day 1 and 8, q3w, combined with nintedanib 200mg twice daily (except day 1 and 8). Again, the patient had an immediate clinical benefit (within 1 week; cough and dyspnoe) and the ECOG raised from 1 to 0. FISH analysis from initial biopsy revealed a non-KIF5B-RET-fusion. This might show a substantial benefit in the preliminary literature. Conclusion: Combination of RET-inhibitor (plus docetaxel) in a patient with PD on RET inhibition resulted in good clinical response in a patient with a non-KIF5B-RET mutation. This case illustrates that treatment with a ’second-line’ TKI (such as nintedanib) can be effective in RET-rearranged NSCLC.

Keywords: RET, KIF5B, cabozantinib, nintedanib

POSTER SESSION 3 – P3.02C: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/IMMUNOTHERAPY
TARGETED THERAPY – WEDNESDAY, DECEMBER 7, 2016

P3.02C-018 COULD COX-2 INHIBITORS ENHANCE THE OUTCOMES OF CHEMOTHERAPEUTIC AGENTS IN LUNG CANCER?
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Background: Lung cancer represents the leading cause of cancer-related deaths worldwide. Novel therapeutic approaches targeting crucial pathways are urgently needed to improve its treatment. Inflammation plays a critical role in multistage tumor development and increased evidence has supported the involvement of cyclooxygenase-2 expression in carcinogenesis. We investigated the potential use of COX-2 inhibitors in cancer proliferation and apoptosis. Methods: Celecoxib, rofecoxib, etoricoxib, meloxicam, ibuprofen and indomethacin were the COX-2 inhibitors included in this study. Docetaxel and Cisplatin are the chemotherapeutic agents that we combined with COX-2 inhibitors. Lung cancer cell lines (NCI-H1048 Small cell lung cancer, A549 Non-small cell lung cancer) were purchased from ATCC LGC Standards. At indicated time-point, following 24h and 48h incubation, cell viability

Keywords: bevacizumab, malignant pleural effusion, efficacy, lung adenocarcinoma

POSTER SESSION 3 – P3.02C: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/IMMUNOTHERAPY
TARGETED THERAPY – WEDNESDAY, DECEMBER 7, 2016

P3.02C-019 The Use of Metformin and the Incidence of Metastases at the Time of Diagnosis in Patients with Lung Cancer and Type 2 Diabetes
Marina Serdarevic1, Suzana Kukulj2, Ante Rebic2, Gordana Drpa2, Bernard Samarzija3, Miroslav Samzarija3
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Background: Lung cancer is often insidious disease. It usually produces only a few symptoms until the disease is advanced. At initial diagnosis 20% of patients have localized disease, 25% of patients have regional metastasis and 55% of patients have distant spread of disease. Metastasis is a process by which a small number of cancer cells undergo numerous alterations, which enables them to form secondary tumors at another and often multiple sites in the host. Recently, studies have suggested that cancer stem cells are the originators of metastasis. Cancer stem cells are small populations of slowly dividing, treatment-resistant, undifferentiated cancer cells that are being discovered in a different cancers. Metformin has proved to be effective in the treatment of glablastoma and neuroblastomas, in vitro, by targeting their cancer stem cell population. Recently, studies have shown that metformin use is not associated with a decreased risk of lung cancer in patients with type 2 diabetes, but it has been suggested that metformin use is associated with improved survival among patients with stage IV NSCLC patients. Methods: The aim of our study was to compare incidence of metastasis in lung cancer patients with metformin patients and patients with lung cancer that were not treated with metformin. It is a retrospective analysis of lung cancer patients diagnosed at our department between January 1, 2012 and December 31 2013. and data were collected from our computerized base. Results: During the two-year period in our department there were 335 newly diagnosed lung cancer patients. Among them there were 25 (7%) patients with diabetes mellitus that were on therapy with metformin prior to lung cancer diagnosis for at least six months. We have proved significant difference between two groups in the incidence of patients with distant spread of disease (stage IV) at the time of diagnosis. Metformin group had a lower incidence of stage IV at the time of diagnosis (44% vs 64%, p=0.041). The results did not reveal a significant difference in total number of patients with distant spread or in the type of metastasis. Conclusion: We have shown that patients that were treated with metformin had lower incidence of distant metastases at the time of diagnosis. Further research should evaluate biologic mechanisms and test the effect of metformin on inhibiting the cancer spread in prospective clinical trials.

Keywords: SCLC, NSCLC, Metastases, metformin

POSTER SESSION 3 – P3.02C: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/IMMUNOTHERAPY
TARGETED THERAPY – WEDNESDAY, DECEMBER 7, 2016

P3.02C-020 MORE THAN 3 YEARS LONG-TERM MAINTENANCE TREATMENT OF BEVACIZUMAB FOR ADVANCED-STAGE NSCLC: A REPORT OF THREE CASES
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Background: Bevacizumab has proven efficacy in extending OS and PFS as first-line treatment for advanced nonsquamous NSCLC. Methods: There were three advanced NSCLC patients received maintenance with bevacizumab for more than 3 years in our hospital, and here we share the data of these patients. Results: All three patients with advanced-stage lung adenocarcinoma received bevacizumab (15mg/kg) plus paclitaxel and carboplatin for 6 cycles as first-line treatment and bevacizumab maintenance. In the maintenance, proteinuria occurred in all three patients after 6 months of treatment or longer and caused cessation of bevacizumab in two patients. It’s noteworthy that two patients presented spleen changes after long-term maintenance. In patient 01, proteinuria occurred after 8 cycles of bevacizumab, caused cessation of 7 doses, and lasted till one year after discontinuation of bevacizumab. In patient 02, splenomegaly was found after 44 cycles of bevacizumab, caused treatment discontinuation, and reversed after 6 months of discontinuation. In patient 03, proteinuria occurred after 29 cycles of bevacizumab and caused cessation of 5 doses of bevacizumab. Besides, increased serum creatinine and blood urea nitrogen were found after 18 months of proteinuria, and CT scan indicated wedge-shaped defects in spleen after 55 cycles. After disease progression or discontinuation of bevacizumab, two patients were confirmed harboring EGFR mutations and received EGFR TKI treatment. The other patient, EGFR mutation and ALK-arrangement negative, received chemotherapy after disease progression.

Conclusion: These patients received bevacizumab maintenance for more than 3 years were all enrolled in clinical trials, and the long-term maintenance brought them adverse effects as well as clinical benefit. In the real world, the cycles of maintenance and the best total dosage of bevacizumab for NSCLC remain uncertain. Is it true that the longer the treatment lasts, the more benefit the patients get with the maintenance treatment of bevacizumab?

Keywords: long-term maintenance, case report, bevacizumab


P3.02C-021 PD 0332991, A Selective Cyclin D Kinase 4/6 Inhibitor, Sensitizes Lung Cancer Cells to Killing by EGFR TKIs

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Background: The acquired resistance of EGFR-TKIs in non-small cell lung cancer (NSCLC) is a big challenge in the targeted therapy. It is necessary to investigate whether CDK4/6 inhibitor PD 0332991 could contribute to reverse the drug resistance of EGFR TKI resistant human lung cancer cell in vitro and in vivo and to explore the underlying mechanisms. Methods: Cell viability, proliferation, cell cycle and apoptosis were measured by MTT assay, EDU assay, cell cycle and apoptosis assay, respectively. The underlying mechanisms were assessed by real-time PCR, western-blot and microarray analysis. Tumor xenograft animal study was performed to verify the effect of PD 0332991 in vivo. Lung adenocarcinoma patients with acquired resistance to EGFR-TKIs were given a tentative treatment of PD 0332991. Results: Our study showed that PD 0332991 could potentiately significantly the gefitinib induced growth inhibition of both EGFR-TKI sensitive PC-9 and EGFR-TKI resistant PC-9/AB2 cells, through down-regulating the proliferation, inducing cell apoptosis and 60/G1 cell cycle arrest. In the mice experiments in vivo, we found the mice treated by PD 0332991 and gefitinib showed a fastest tumor regression, and a most delayed relapse pattern. The tumor from the mice treated by the combination showed a significantly down-regulated proliferation, an up-regulated apoptosis and a less angiogenesis confirmed by Ki67, TUNEL and CD34 staining, respectively. Conclusion: Our research showed, for the first time, that PD 0332991 could contribute EGFR-TKI resistant NSCLC cells to overcome the acquired resistance in vivo and in vitro. This might provide a novel treatment strategy for the patients with EGFR-TKI resistance.


P3.02C-022 Anticancer Activity of Sorafenib in Combined Treatment with Betulin in Human Non-Small Cell Lung Cancer Cell Lines

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Background: The highly selective multi-targeted agent sorafenib is an inhibitor of a number of intracellular signaling kinases with anti-proliferative, anti-angiogenic and pro-apoptotic effects in various types of tumors, including human non-small cell lung cancer (NSCLC). Betulin displays a broad spectrum of biological and pharmacological properties including the anticancer and chemopreventive activity. Combination of drugs with different targets is a logical approach to overcome multilevel resistance. The aim of the study was to evaluate the anticancer activity of sorafenib in combination with betulin in human non-small cell lung cancer cell lines (A549 and HCC827) in vitro.

Methods: Sorafenib and betulin were tested in combination in a panel of human non-small cell lung cancer cell lines (A549 and HCC827) in vitro.

Results: Combination of sorafenib and betulin resulted in increased growth inhibition, induction of apoptosis and cell cycle arrest compared to single agents. The combination treated A549 cells increased the number of cells in G0/G1 phase and decreased the number of cells in S phase. The combination treatment increased the number of apoptotic cells, apoptosis was induced by both intrinsic and extrinsic pathways. Sorafenib and betulin treatment increased the expression of pro-apoptotic proteins, caspase-3, caspase-7 and BAX, and decreased the expression of anti-apoptotic proteins, BCL-2 and BCL-XL. The combination treatment of sorafenib and betulin increased the expression of pro-apoptotic proteins and decreased the expression of anti-apoptotic proteins.

Conclusion: Combination of sorafenib and betulin showed significant synergistic effect on the growth inhibition and induction of apoptosis and cell cycle arrest in human non-small cell lung cancer cell lines. The combination treatment increased the expression of pro-apoptotic proteins and decreased the expression of anti-apoptotic proteins.
cross-stimulation among key pathways in NSCLC progression. Methods: The NSCLC cell lines A549, H358, A427, HCC827, H1703, normal lung microvascular endothelial cells HLMC and normal human PBMC were treated with sorafenib and betulinic acid alone and in combination. We examined the effect of different combined treatment on viability (MTS test), proliferation and apoptotic susceptibility analyzed by flow cytometry, alterations in signaling pathways by western blotting and as well colony-forming ability. Results: The combination of sorafenib with betulinic acid had strong effect on induction of apoptosis of different non-small cell lung cancer cell lines but not effect on normal cells. Combination treatment inhibited phosphorylation of ERK, AKT and mTOR in the A549 cell lines and in low concentrations significantly reduced the colony-forming ability of A549, H358 and A427 cells as compared to either compound alone. Conclusion: In this study we show that sorafenib significantly suppressed the proliferation of lung cancer cells and treatment with the combination of low concentrations of sorafenib with betulinic acid exhibited ability to induce a high level of cell death in some non-small cell lung cancer cell lines.

Keywords: Natural products, non-small cell lung cancer, Targeted therapy, Tyrosine kinase inhibitors

POSTER SESSION 3 – P3.02C: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/ IMMUNOTHERAPY TARGETED THERAPY – WEDNESDAY, DECEMBER 7, 2016

P3.02C-023 MUTATION AND PROGNOSTIC ANALYSES OF PIK3CA IN PATIENTS WITH COMPLETELY RESECTED LUNG ADENOCARCINOMA
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Background: PIK3CA mutation represents a clinical subset of diverse carcinomas. We explored the status of PIK3CA mutation and evaluated its genetic variability, treatment and prognosis in patients with lung adenocarcinoma. Methods: A total of 810 patients with completely resected lung adenocarcinoma were recruited between 2008 and 2013. The lines with PIK3CA mutation and other three genes, i.e. EGFR mutation, KRAS mutation & ALK fusion, was examined by reverse transcription-polymerase chain reaction (RT-PCR). Survival curves were plotted with the Kaplan-Meier method and log-rank for comparison. Cox proportional hazard model was performed for multivariate analysis. Results: Among the 810 patients, 23 cases of PIK3CA mutation were identified with a frequency of 2.8%. There were 14 males and 9 females with a median age of 61 years. Seventeen tumors revealed concurrent gene abnormalities of EGFR mutation (n=12), KRAS mutation (n=3) and ALK fusion (n=2). Seven patients with EGFR & PIK3CA mutations received the dosing of EGFR-TKIs yielded a median progression free-survival of 6.0 months. Among 6 evirouchem-treated patients, stable disease was obtained in three patients with a median PFS of 3.5 months. Patients with and without PIK3CA mutation had different overall survivals (32.2 vs. 49.6 months, P=0.003). Multivariate analysis revealed that PIK3CA mutation was an independent predictor of poor overall survival (HR=2.37, P=0.017). Conclusion: The frequency of PIK3CA mutation was around 2.8% in Chinese patients of lung adenocarcinoma. PIK3CA mutation was associated with reduced PFS of EGFR-TKIs treatment and shorter overall survival.

Keywords: overall survival, PIK3CA mutation, frequency, treatment

POSTER SESSION 3 – P3.02C: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/ IMMUNOTHERAPY TARGETED THERAPY – WEDNESDAY, DECEMBER 7, 2016

P3.02C-024 DETECTION OF NOVEL ACTIVATING FGFR REARRANGEMENTS, TRUNCATIONS, AND SPICE SITE ALTERATIONS IN NSCLC BY COMPREHENSIVE GENOMIC PROFILING
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Background: Activation of the fibroblast growth factor receptor (FGFR) family through mutation, amplification, C-terminal truncation, and fusion has been described in multiple cancer types, and FGFR inhibitors are currently being evaluated in the clinic. Though FGFR1 amplification has been defined in several datasets, other FGFR alterations in NSCLC are not well defined. Methods: Hybrid-capture based comprehensive genomic profiling (CGP) was performed on 13,898 consecutive FFPE lung cancer specimens (adeno 71%, squamous 12%) to a mean coverage depth of >650X for genes plus 315 cancer-related genes. Results: We used the Geneia software to identify and analyze rearrangements or splice site mutations resulting in intact kinase domain (KD). The median age was 63 years old (range 36-83 years). Patients with these alterations were 60% (26/53) male, and 72% (31/43) with available data were stage IV. 26 patients (49%) had adenocarcinomas and 18 patients (34%) had squamous histology. FGFR alterations identified included 19 FGFR3-TACC3 fusions, one FGFR2-KIAA1598 fusion, and 7 novel fusions involving FGFR2, FGFR3 or FGFR4. We also identified 16 cases with C-terminal truncations resulting in loss of exon 18, but retention of the KD, 9 cases with mutations predicted to result in alternative splicing in the FGFR extracellular domain (exons 3 or 4), and one case with deletion of exons 3-6. Genomic analysis revealed concurrent FGFR amplification in 13% (753) of cases. Co-occurring alterations were observed in known drivers including EGFR, ERBB2, MET, and BRAF in 15% (of 53) cases, and KRAS mutation in an additional 15% (9/53) of cases. The average tumor mutation burden in cases with these FGFR alterations was relatively high (mean 16.9 mutations/Mb, median 10.1 mutations/Mb, range 0.9-86.5 mutations/Mb) as compared to a mean of 5.2 mutations/Mb in NSCLCs. One patient with a novel FGFR2-LZTFL1 fusion had a partial response to the pan-FGFR inhibitor (JN)-42756493 and remained progression free for 11 months. Conclusion: Diverse FGFR alterations were detected using CGP in 0.4% of NSCLCs. Of the 53 cases identified, 37 (70%) were negative for other known driver alterations. In cases with co-occurring drivers, including two with EGFR exon 19 deletion, the possibility of FGFR fusion in the setting of acquired resistance will be evaluated. One patient with a novel FGFR2 fusion had clinical benefit from an investigational FGFR inhibitor, suggesting that these alterations may predict response to targeted therapies.

Keywords: FGFR, (JN)-42756493, Rearrangements, Targeted

POSTER SESSION 3 – P3.02C: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/ IMMUNOTHERAPY TARGETED THERAPY – WEDNESDAY, DECEMBER 7, 2016

P3.02C-025 SAFETY AND EFFICACY OF APATINIB IN PATIENTS WITH PREVIOUSLY HEAVILY TREATED ADVANCED NON-SQUAMOUS NON-SMALL-CELL LUNG CANCER
Feng Ying Wu, Shi Jia Zhang, Sheng Xiang Ren, Caicun Zhou
Medical Oncology, Shanghai Pulmonary Hospital, Tongji University, Shanghai/China

Background: Apatinib is a tyrosine kinase inhibitor which selectively inhibits VEGFR-2 and also represents mild inhibition to PDGFR, c-Kit and c-scr. It is an orally bioavailable, small molecular agent which is thought to inhibit angiogenesis and tumor cell proliferation. Previous clinical trials have demonstrated its obvious antitumor activity in various cancer type. Thus we designed this phase II, open-label, single-armed, prospective study (NCT02515435) to investigate the efficacy and safety of apatinib for heavily treated, advanced non-squamous NSCLC patients who are not applicable to current standardized therapy or other clinical trials. Methods: We prospectively enrolled 40 patients with previously heavily treated advanced non-squamous NSCLC. All patients received apatinib with a dose of 500mg, q.d., p.o. Efficiency was evaluated initially 4 weeks later and then every 8 weeks until disease progression, death, or unacceptable toxicity. The primary end point of this study was overall response rate (ORR). The secondary end points were progression-free survival (PFS), overall survival (OS). Results: Forty patients were enrolled in the study with a median age of 61. 15% of patients received apatinib as second-line therapy, 40% of patients received apatinib as third-line therapy, and 60% as forth-line to twelfth-line therapy. Nine patients were found with activated EGFR mutation. Among all the enrolled patients, 38 patients had clinical evaluation and the other 2 received second treatment of apatinib less than one month. Within 33 patients who had available image efficiency, 6 were identified as PR,17 SD and 10 PD, no CR was observed. The ORR was 18.18 %, the DCR was 69.69 %. The ORR for patients with EGFR mutation positive and negative were 25% and 16% separately. The median PFS was 3.22 months (95% CI, 2.26-2.44 months). Among them, 6 patients received the treatment of apatinib more than five months. The 6-month OS rate was 76.98% (95% CI, 61.68%-92.27%), the 12-month OS rate was 57.48% (95% CI, 28.75%-86.20%). Common treatment-related adverse events were proteinuria (25%), hypertension (17.5%), and hand-foot-skin reaction (HFSR)(27.3%). Severe adverse events included grade 3 hypertension

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Abstracts

POSTER SESSION 3 – P3.02: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/ IMMUNOTHERAPY
IT – WEDNESDAY, DECEMBER 7, 2016

P3.02C-027 PHASE I AND PK STUDY OF THE FOLATE RECEPTOR-TARGETED SMALL MOLECULE DRUG CONJUGATE (SMDC) EC1456 IN ADVANCED CANCER: LUNG CANCER SUBSET
Martin Edelman1, Jasgit Sachdev2, Wael Harb3, Allison Armour4, Ding Wang5, Linda Garland6
1Greenebaum Cancer Center, University of Maryland, Baltimore/United States of America, 2Virginia Piper Cancer Center, Scottsdale/ AZ/United States of America, 3Horizon Cancer Center, Lafayette/IN/United States of America, 4Endocyte, Lafayette/AL/United States of America, 5Josephine Ford Cancer Institute, Detroit/MI/United States of America, 6University of Arizona, Tucson/AL/United States of America

Background: EC1456 is composed of folate acid conjugated through a releasable linker system to a potent microtubule inhibitor, tubulysin B hydrazide. EC1456 targets folate receptor (FR)-expressing cancer cells, which occur in approximately 60% of NSCLC cases and 14% of SCLC. Methods: The objectives of the ongoing Phase 1 are to determine the safety, PK, and optimal dosing schedule of EC1456 in advanced cancer pts. FR expression (not required for enrollment) is characterized in all pts using 11C-ethylfolate. Results: 63 pts were dosed weekly (QW) or twice-weekly (BIW), for 2 consecutive weeks of a 3-week cycle. 8 NSCLC and 3 SCLC pts received doses ranging from 1.0-12.5 mg/m². Toxicities are primarily Grade (Gr) 1 and 2. Common adverse events (AE) are GI, fatigue, and metabolic changes. Gr 3 infusion reaction (4.5 mg/m²) and Gr 3 headache (10.0 mg/m²) were seen in the QW cohort. The safety profile in lung cancer pts was similar to the overall population.

Response and durability of response is demonstrated in the figure:

<table>
<thead>
<tr>
<th>BIW (N=32)</th>
<th>QW (N=31)</th>
<th>BIW Lung (N=4)</th>
<th>QW Lung (N=7)</th>
</tr>
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<tbody>
<tr>
<td>All</td>
<td>Drug Related</td>
<td>All</td>
<td>Drug Related</td>
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<tr>
<td>≥ 1 AE</td>
<td>32</td>
<td>(100%)</td>
<td>25</td>
</tr>
<tr>
<td>≥ 1 Gr 3 or 4 AE</td>
<td>9</td>
<td>(59%)</td>
<td>6</td>
</tr>
<tr>
<td>≥ 1 Serious AE</td>
<td>12</td>
<td>(38%)</td>
<td>2</td>
</tr>
</tbody>
</table>

Serious drug related AEs: Constipation (2/63 pts); Abdominal pain, Anemia, Headache, Infusion reactions, and SVT(1/63 pts each)

Keywords: EC1456, FR, lung cancer, Phase I, PK, tumor biology,umbles, tolerability, LCSR

POSTER SESSION 3 – P3.02C: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/ IMMUNOTHERAPY
IT – WEDNESDAY, DECEMBER 7, 2016

P3.02C-026 IS NIVOLUMAB SAFE AND EFFECTIVE IN ELDERLY AND PS2 PATIENTS WITH NON-SMALL CELL LUNG CANCER (NSCLC)? RESULTS OF CHECKMATE 153

David Spiegel1, Lee Schwartzberg2, David Waterhouse3, Jason Chandler4, Maen Hussein5, Robert Jotte6, Edward Stepanski7, Michael McLeod8, Ray Page9, Rohini Sen10, Jeffrey McDonald11, Kelly Bennett12, Beata Korytkowsky13, Nivedita Anaur14, Craig Reynolds15
1Sarah Cannon Research Institute/tennessee Oncology, PLLC, Nashville/TN/United States of America, 2The West Cancer Center, Memphis/TN/United States of America, 3Oncology Hematoday Care, Cincinnati/Ohio/United States of America, 4Florida Cancer Specialists, Leesburg/FL/United States of America, 5Rocky Mountain Cancer Centers, Denver/CO/United States of America, 6Vector Oncology, Memphis/TN/United States of America, 7Florida Cancer Specialists, Cape Coral/FL/United States of America, 8The Center for Cancer and Blood Disorders, Fort Worth/TX/United States of America, 9Adelphi Values, Boston/MA/United States of America, 10Bristol-Myers Squibb, Princeton/New Jersey/United States of America, 11Ocala Oncology Center, Ocala/FL/United States of America

Background: CheckMate 153 (NCT02066636) is an ongoing, predominantly community-based, phase 3B/4 safety study of nivolumab in patients with previously treated metastatic NSCLC in the US/Canada. Here we report safety, efficacy, and patient-reported outcome (PRO) data for subgroups of patients aged ≥70 years or with a poor baseline ECOG PS (PS2). Methods: Patients were enrolled in four subgroups based on histology and prior regimen number; one subgroup enrolled patients with squamous (SQ) or non-SQ NSCLC, PS2, and ≥1 prior therapies. Data on elderly patients were pooled across subgroups. The primary objective was assessment of high-grade (grade 3-4 and 5) select (those with a potential immunologic cause) treatment-related AE (TRAE) incidences. Exploratory endpoints included efficacy, biomarkers, pharmacokinetics, and PROs. Results: Of 1,308 patients, 520 (40%) were aged ≥70 years and 108 (8%) had PS2. TRAE incidences for the age and PS subgroups were comparable with those for the overall population (table), as were select TRAE incidences for the subgroups. Estimated 6-month OS was lower with PS2 (10.6 vs 16.3 months, p=0.09), but similar between age subgroups and the overall population (table). Early PRO data revealed significant improvements overall in both age subgroups using LCSST and EQ-5D-5VS, with younger patients showing greater improvement on some scales. Patients with SQ disease and PS2 generally reported stable quality-of-life/symptom control, whereas patients with non-SQ disease had statistically significant improvements on most scales. Updated data, including 1-year OS, will be presented. Conclusion: In this large study of advanced, previously treated, predominantly community-based patients with NSCLC, the nivolumab safety profile for age and PS subgroups were comparable with those for the overall population and from prior nivolumab NSCLC studies. OS was similar in younger and older patients, but lower in PS2 patients at early time points. Nivolumab appears to have similar risks/benefits in older and poorer PS patients as in the general population.

<table>
<thead>
<tr>
<th>&lt;70 years (n = 728)</th>
<th>≥70 years (n = 520)</th>
<th>PS2 (n = 1,175)</th>
<th>PS2 (n = 108)</th>
<th>Overall (n = 1,308)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRAE, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any grade</td>
<td>401</td>
<td>(55)</td>
<td>321</td>
<td>(62)</td>
</tr>
<tr>
<td>Grade 3-4</td>
<td>89</td>
<td>(11)</td>
<td>65</td>
<td>(12)</td>
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<tr>
<td>Grade 5</td>
<td>3</td>
<td>(&lt;1)</td>
<td>1</td>
<td>(&lt;1)</td>
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Keywords: Nivolumab, elderly, performance status, Patient-reported outcomes

Keywords: Nivolumab, elderly, performance status, Patient-reported outcomes
Conclusion: EC1456 is well tolerated, with early indications of efficacy suggested by durable stable disease, and responses in this refractory population. Updated safety, PK, and efficacy data will be presented at the meeting.

Keywords: Folate receptor, Small molecule Drug Conjugate, EC1456

References

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Background: In randomized trials of nivolumab in NSCLC, less than 10% of pts had poor performance status (Eastern Cooperative Oncology Group Performance Status [ECOG PS]) of 0-1. The effectiveness of nivolumab in elderly pts with NSCLC treated in routine practice has not been previously described. Methods: We conducted a retrospective cohort study of pts with advanced NSCLC treated with nivolumab outside of clinical trials at the University of Pennsylvania between March 2015 and March 2016. Logistic regression and Cox proportional hazards models were used to estimate the association of age (≥75 vs. <75 years) with overall response rate (ORR), progression-free survival (PFS), and overall survival (OS), adjusting for ECOG PS (0-1 vs. ≥2), sex, smoking history (heavy [≥10 pack-years] vs. light/never [≤10 pack-years]), and number of prior systemic therapies (1 vs. ≥2). Results: Of 175 pts treated with nivolumab, 43 (25%) were ≥75 years old and 42 (24%) had ECOG PS ≥2. Ninety-five pts (54%) were female, 147 (84%) had heavy smoking history, and 81 (46%) had received ≥2 prior systemic therapies: ORR was 19.4%, with median PFS and OS of 2.1 and 6.5 months, respectively. Age ≥75 years was not associated with ORR (OR 1.0, 95% CI 0.6-2.5, p=0.97), PFS (HR 0.71, 95% CI 0.5-1.1; p=0.12), or OS (HR 0.8, 95% CI 0.5-1.4; p=0.4). ECOG PS ≥2 was associated with lower ORR (71% vs. 23.3%; OR 0.25, 95% CI 0.07-0.88; p=0.03), inferior PFS (median 1.8 vs. 2.3 months; HR 1.9, 95% CI 1.3-2.8; p=0.001), and inferior OS (median 3.6 vs. 7.8 months; HR 2.6, 95% CI 1.6-4.1; p=0.001).

Conclusion: In a large NSCLC cohort treated outside of clinical trials, elderly pts gained similar benefit from nivolumab compared to younger pts. Pts with poor performance status had inferior outcomes regardless of age.

Keywords: Nivolumab, Immunotherapy, elderly, non-small cell lung cancer

References

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Background: Immunologic checkpoint inhibitors are associated with immune-related adverse events (irAEs). While the incidence of irAEs in routine practice and their effect on outcomes have been well characterized in melanoma, a similar analysis has not been previously reported in NSCLC pts treated with anti-programmed death 1 (PD-1) therapy. Methods: We conducted a retrospective cohort study of pts with advanced NSCLC who received nivolumab outside of clinical trials between March 2015 and March 2016 at the University of Pennsylvania. irAEs were graded using the Common Terminology Criteria for Adverse Events version 4.0. Data collected included demographics, timing and treatment of irAEs, and dates of disease progression and death or last follow-up. To analyze the effect of irAEs on progression-free survival (PFS) and overall survival (OS), landmark analyses were used beginning from 3 months after start of treatment. Pts who reached the PFS or OS endpoints prior to 3 months were excluded. Cox proportional hazards models were used to assess for differences in PFS and OS according to the occurrence of an irAE, adjusting for age, sex, and Eastern Cooperative Oncology Group Performance Status (ECOG PS). Results: 175 pts received a median of 5 cycles of nivolumab (range, 1-24, IQR, 1-9). Median age was 68 years (range, 38-85, IQR, 60-74). Forty-six percent of pts were male; 55% had an ECOG PS ≥2. Twenty-five (14%) pts (16%) experienced an irAE of any grade and 63% (3%) had a grade 3/4 irAE. Median time to onset of the irAE was 3 cycles (range, 1-18, IQR, 2-6). Of the pts who experienced an irAE, 14 (50%) were treated with systemic corticosteroids. The most common irAEs were hypothyroidism/hyperthyroidism (n=8), pneumonitis (n=5), colitis (n=4; grade 3, colitis (n=4; grade 3), dermatitis (n=4), and arthritis (n=2). Less common irAEs (n=1 each) included hepatitis (n=1, gastrointestinal (n=1) and hypophysitis (n=1), hypophysitis (n=1)). Overall response rate was 19.4% (34 of 175), and median PFS and OS were 2.1 and 6.5 months, respectively. After adjusting for age, sex, and ECOG PS, landmark analyses revealed no difference in PFS (HR 1.3, 95% CI 0.4-3.8, p=0.7) or OS (HR 0.9, 95% CI 0.3-2.7, p=0.9) stratified by the presence or absence of an irAE. Conclusion: In NSCLC pts treated with nivolumab in typical practice, irAEs of any grade were uncommon, and grade 3/4 irAEs were rare. The occurrence of irAEs was not associated with PFS or OS.

Keywords: Nivolumab, non-small cell lung cancer, immune-related adverse events
Background: Previous analyses showed no clinically significant exposure- efficacy relationship for pembrolizumab doses of 2-10 mg/kg. Population pharmacokinetics (popPK) modeling suggested weight-based or fixed pembrolizumab doses could maintain exposures within the established safety/ efficacy bounds. Fixed dose advantages include increased convenience, reduced dosing error risk, and less discarded product. Pembrolizumab 200 mg Q3W was evaluated in the KEYNOTE-024 study of pembrolizumab versus platinum-doublet chemotherapy for treatment-naive advanced NSCLC with PD-L1 TPS ≥50% (NCT02142738). Methods: Pembrolizumab serum concentration was quantified with an electrochemiluminescence-based immunoassay (lower limit of quantification, 10 ng/mL). The existing 2-component popPK model derived from studies of weight-based pembrolizumab dosing was extended with KEYNOTE-024 concentration-time data. Correlation between pembrolizumab exposure (ie, area under the serum-concentration curve over 6 weeks [AUCss-6weeks]) and efficacy was assessed. Results: Median (range) weight was 69.7 kg (38-110) in KEYNOTE-024 and 75 kg (35.7-210) in the existing popPK model studies. In treatment-naive advanced NSCLC, there was a flat relationship between pembrolizumab exposure and efficacy for the 200-mg fixed dose and weight-based doses (linear regression P > 0.05). Observed pembrolizumab concentrations for 200 mg (median 1976 μg/mL, 90% CI 1174-3322) were consistent with predictions (median 1751 μg/mL, 90% prediction interval 955-3136) and fell within the previously observed therapeutic window for 2 and 10 mg/kg (Figure). There was considerable overlap in exposures for 2 mg/kg and 200 mg, regardless of whether weight was >90 or <90 kg for 200 mg (Figure).

Conclusion: Pembrolizumab exposure at 200 mg Q3W is similar to that of 2 mg/kg Q3W. Including data from patients with advanced NSCLC treated with 200 mg did not change the flat exposure-efficacy relationship. Along with the superior PFS and OS provided by pembrolizumab over platinum-doublet chemotherapy as first-line therapy for advanced NSCLC with TPS ≥50%, these data support 200 mg Q3W as an alternative to the approved 2-mg/kg Q3W dose.

Keywords: pembrolizumab, pharmacokinetics, dosing

Background: In non-squamous NSCLC PD-L1 negative patients (pts), IC might increase the risk of early death compared to docetaxel in the phase III study CheckMate 057. Tumor Growth Rate (TGR) is calculated using 2 CT scans and the time interval between the 2 exams. It integrates tumor dynamics and kinetics. We hypothesized that TGR could identify a subset of pts named PPD, in which IC could accelerate tumor progression, leading to early death. Methods: We performed a retrospective case study of all NSCLC pts treated by IC in a single institution between Dec. 12 and Feb. 16. CT scan were centrally reviewed by a senior radiologist and assessed according to RECIST 1.1 criteria. We calculated TGR at baseline of IC (baseline CTscan [n=ns-1CTscan] and TGR during IC [n+2 CTscan vs n+1 CTscan]). We further estimated the difference (deltaTGR) between TGR during IC and TGR at baseline. DeltaTGR>0 means IC speeds up tumor growth. PPD was defined as deltaTGR>50%, corresponding to an absolute increase in TGR greater than 50% per month. PDL1 expression was assessed with the SP142 clone. Results: 89 pts were eligible. 58% were male, median age 60 (41-78), 15% never smokers. 62 pts had adenocarcinoma, 21 squamous and 6 other histologies. Mutational status was unknown for 14 pts; 35% wild type, 9 pts EGFRmut, 25 pts KRASmut. PDL1 expression was positive in 44 pts, unknown in 57 pts, 52 pts (58%) received nivolumab, 25 pembrolizumab and 12 atezolizumab. Treatment was received as 1-3rd line in 52 pts, and as ≥4th line in 37 pts. Overall, 25 pts (28%) had a response according to RECIST 1.1 criteria, 31 (35%) a stable disease. Median OS was 14.7 months. During IC, deltaTGR was <0 in 79 pts and >0 in 20 pts. Among the 20 pts with deltaTGR>0, 9 had a PPD. Characteristics (age, sex, smoking status, pathology, number of previous line, PDL1 status) of the 9 pts were not different from other pts. None of the PPD were pseudoprogression. Median OS of PPD vs others was 3.2 and 23 months, respectively. PPD was not more frequent in tumors with high baseline TGR. Conclusion: Our results suggest that PPD is a new subset of response criteria in which IC may increase tumor progression, leading to a poorer survival. Rapidly growing disease at study entry or RECIST criteria could predict the occurrence of PPD.

Keywords: Tumor growth rate, non small cell lung cancer, Immune checkpoint inhibitors

P3.02C-032 INTERSTITIAL PNEUMONITIS ASSOCIATED WITH IMMUNE CHECKPOINT INHIBITORS TREATMENT IN CANCER PATIENTS

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Background: Immune checkpoint inhibition therapy is now a standard of care in melanoma, lung cancer and is spreading across other tumours. Immune checkpoint inhibitors (ICI) are generally well tolerated but can also generate immune-related adverse effects. Since the first trials, pneumonitis has been identified as a rare but potentially life-threatening event. Methods: We conducted a retrospective study over a period of 2 years. Data on IC use in clinical trials, access programs or following national approval. We report the main features of possibly related pneumonitis occurring in patients treated with ICI with a particular focus on clinical presentation, radiologic patterns (with a double reviewing by radiologists and pulmonologists) and histology/pathology and therapeutic strategies. Results: We identified 71 patients with possibly related pneumonitis including 54 NSCLC and 13 melanoma. They mainly received PDI inhibitors. Pneumonitis usually occurred in male, former or current smokers with a median age of 53 years. We observed grade 2 (n=46, 62.5%) and grade 3 (n=6, 7.9%) pneumonitis. The median duration time between the introduction of immunotherapy and the pneumonitis was 2.2 months (0.1-27.4). Ground glass opacification on lung CT scan were the
most prevalent lesion 80.9% (n=55), followed by consolidations 44.1% (n=30), reticulations 36.7% (n=25) and bronchiectasis in 20.6% (n=14). When performed, bronchoalveolar lavage (BAL) showed a T-lymphocytic alveolitis and transbronchial biopsy an inflammatory and lymphatic infiltrate. Pneumonitis treatment was steroids (86.6%) and/or antibiotics (67.6%). Immunotherapy was stopped after the pneumonitis for 65 cases (92.9%) and reintroduced for 12 (9.4%) cases. Twenty-four patients (34.3%) were dead at the last follow-up and 46 patients (65.7%) were still alive. Among the living patients, the pneumonitis outcome was a total recovery in 12 patients, improvement in 22 patients, stability in 10 patients, worsening evolution in 1 patient (unknown). Causality of immunotherapy was evaluated by investigators as “possible” for 34 patients (49.3%), “probable” for 17 (24.6%), “certain” for 15 (21.7%) other causes for 3 (4.3%) and 2 unknowns. Median overall survival from the onset of pneumonitis was 6 months. Conclusion: This serie, the largest to date, of immune-related pneumonitis demonstrates that it occurs usually during the first months and displays specific radiologic features. As there is no clearly identified risk factor, oncologists should be able to detect, diagnose (with CT-scan and bronchoscopy) and treat this adverse event. An early diagnosis is essential in order to avoid severe consequences. Such an observation shows that pneumonitis is usually associated with a favorable outcome and requires a close collaboration between pulmonologists, radiologists and oncologists.

Keywords: Melanoma, interstitial pneumonitis, Immunotherapy, lung cancer

P3.02C-033 PATTERN'S OF PROGRESSION AND MANAGEMENT OF ACQUIRED RESISTANCE TO ANTI-PD-1 ANTIBODIES IN ADVANCED NON-SMALL-CELL LUNG CANCER

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Background: Anti-PD-1 antibodies (pembrolizumab and nivolumab) have shown improved overall survival in second-line treatment for metastatic non-small-cell lung cancer (NSCLC). However, durable responses are rare, and acquisition of resistance remains a challenge to treat. We aimed to assess the pattern of disease progression amongst patients who initially responded to anti-PD-1 agents and their subsequent management. Methods: We retrospectively assessed all patients who commenced single-agent anti-PD-1 antibodies between June 2012 and February 2016 at a single centre. Radiological responses were assessed by the investigator using RECIST 1.1 and irRC. Progressive disease (PD) patterns were defined as solitary, oligometastatic (2-3 lesions), generalised (>3 lesions), enlargement of existing or new lesions, visceral or non-visceral. Management and survival after progression were examined. Results: A total of 81 patients received single-agent pembrolizumab (N=43) or nivolumab (N=38). Of the seventeen (21.3%) patients achieving partial response, three were treatment-naive, fifteen (88.2%) were former or current smokers, none had EGFR mutation or ALK translocation. The median number of disease sites at baseline was fifteen (88.2%) were former or current smokers, none had EGFR mutation

Keywords: Immunotherapy, PD1, NSCLC.
Total 41 patients were analyzed, most of patients (80.5%) received anti-PD-1 agents (pembrolizumab or nivolumab) and 6 patients were treated with anti-PD-L1, atezolizumab, 2 patients received combination treatment with pembrolizumab and tremelimumab. Two patients showed pseudoprogression followed by regression per RECIST v1.1 not per irRC. 4 patients with progression disease per RECIST v1.1 were partial response per irRC, objective response was 29.2% per RECIST v1.1 and 34.1% per irRC, respectively. There was no significant difference in response rate between two methods (p=0.923). The median duration of follow-up was 19.8 months, and the median progression-free survival of all patients was 4.5 months (95% CI 2.7-6.3).

Conclusion: These results suggest that pseudoprogression is not frequently observed in NSCLC, and conventional RECIST v1.1 might underestimate the benefit of immune check point inhibitors. Given the small number of patients studied and short-term follow-up, further study will be warranted whether treatment with immune checkpoint inhibitor beyond RECIST progression can be benefit to patient with advanced NSCLC.

Keywords: immune checkpoint inhibitor, immune related response, non-small cell lung cancer

POSTER SESSION 3 – P3.02C: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/IMMUNOTHERAPY
IT – WEDNESDAY, DECEMBER 7, 2016

P3.02C-036 MANAGEMENT OF EARLY DISEASE PROGRESSION DURING TREATMENT OF ADVANCED NON-SMALL CELL LUNG CANCER WITH NIVOLUMAB
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Background: Immune check point inhibitors have recently become a cornerstone of the management of advanced non-small cell lung cancer (NSCLC). The peculiar mechanism of action of this drug class implies the possibility of early PD during treatment with nivolumab (PD) on the basis of parameters such as the observation of clinical benefit or mild progression at computed tomography scan (CT-scan); however, a guideline for managing early PD during cancer immunotherapy has not been clearly defined yet. The aim of this study is to evaluate the approaches to patients experiencing early PD during treatment with nivolumab for advanced NSCLC.

Methods: Patients treated with nivolumab (3 mg/Kg every 4 days) for advanced NSCLC between April 2015 and May 2016 within a single-institutional translational research study conducted in the San Martino Hospital – National Institute for Cancer Research, Genoa, Italy (approved by the local ethical committee) were considered eligible if their first response assessment (after 4 cycles) was PD. The response evaluation criteria in solid tumors (RECIST) and the immune-related response criteria (irRC) were employed. Since irRC imply the confirmation of PD after 2 further cycles, a cut-off of 6 cycles was set to define the patients who continued nivolumab beyond progression. Results: Globally, 31 patients were eligible: median age=60 years (50-81); males/females=74%/26%; current or former smokers=90%; non-squamous/squamous histology=67%/33%; 25 patients had PD as first evaluation with both criteria, while 4 had PD only with RECIST and 2 had PD only with irRC. With RECIST, 35% of the patients received nivolumab beyond progression (median=10 cycles) and 80% of such patients were alive at the time of the analysis; on the contrary, only 53% of the patients who discontinued nivolumab at PD were still alive at the time of the analysis. With irRC, 30% of the patients received nivolumab beyond progression (median=10 cycles) and 75% of such patients were alive at the time of the analysis, compared to only 47% of the patients who discontinued nivolumab at PD. The decision of continuing nivolumab beyond PD was based on the reported clinical benefit (67%), on the observation of a very limited progression at the CT-scan (22%) or on discordance between response criteria (11%). Conclusion: Administering nivolumab beyond progression might influence the outcomes of selected patients. Additional parameters for discriminating which patients are going to benefit from nivolumab continuation need to be investigated.

Keywords: progressive disease, non-small cell lung cancer, Nivolumab

POSTER SESSION 3 – P3.02C: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/IMMUNOTHERAPY
IT – WEDNESDAY, DECEMBER 7, 2016

P3.02C-037 CLINICAL SAFETY OF COMBINATION THERAPY OF IMMUNE CHECKPOINT INHIBITORS AND VISCUM ALBUM L. IN PATIENTS WITH ADVANCED OR METASTASIZED CANCER
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Background: Newly approved anti-PD-1/PD-L1 and anti-CTLA-4 immune checkpoint monoclonal antibodies (ICM) significantly improve overall survival in advanced or metastasized melanoma and lung cancer. Viscum album L. (VA) may improve survival and supports health related quality of life in cancer patients. The primary objective of the present study was to determine the safety profile of combinatory ICM/VA therapy in advanced or metastasized cancer. Methods: Safety of ICM/VA therapy was examined in an observational open phase IV study in a certified Oncology Centre. ICM or combinational ICM/VA therapies were applied in patients with progressive or metastasized cancer (non-small cell lung cancer or melanoma) in an integrative oncology setting. Toxicity rates of both therapy groups were compared. Evaluation of disease response was performed. Results: A total of 10 cancer patients were treated with nivolumab (75%), ipilimumab (19%) or pembrolizumab (6%). The median age of the study population was 64 years; 64% were male. 11 patients were diagnosed with lung cancer (69%), 4 patients with malignant melanoma (25%) and one patient with a pleural mesothelioma (6%). 9 patients received VA (ICM: 56%); 5 received VA during ICM treatment (ICM: 44%). The adverse event rate for patients treated with combinational ICM/VA was not statistically different from the rate in patients treated with ICM therapy alone (67% vs. 71%, p = 0.060). 73% of adverse events in the ICM/VA group were suspected ICM reactions according to SmPCs. 19% of the total patient cohort showed partial disease response to ICM therapy in line with reported rates in literature. No statistical significant differences were seen between both groups with respect to partial disease response (ICM/VA: 22% vs. ICM: 14%, p = 0.999) and stable disease rates (ICM/VA: 33% vs. ICM: 86%; p = 0.060). Conclusion: This is the first study evaluating the clinical safety profile of immune checkpoint inhibitors in combination with VA in patients with advanced or metastasized cancer. These results indicate that concomitant VA application may not alter adverse event rates in patients treated with nivolumab, ipilimumab or pembrolizumab. Positive ICM-induced disease response has been maintained during additive VA therapy. Adverse event rates and partial disease response rates of the present study were within the range of reported rates. Further prospective studies in larger study cohorts should focus on the assessment of clinical efficacy, pharmacology and quality of life in patients with combinational ICM/VA therapy.

Keywords: Viscum album L., safety profile, immune checkpoint inhibitor, Targeted therapy

POSTER SESSION 3 – P3.02C: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/IMMUNOTHERAPY
IT – WEDNESDAY, DECEMBER 7, 2016

P3.02C-038 FIRST-LINE ATEZOLIZUMAB PLUS CHEMOTHERAPY IN CHEMOTHERAPY-NAÏVE PATIENTS WITH ADVANCED NSCLC: A PHASE III CLINICAL PROGRAM
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Background: First-line treatments for patients with advanced NSCLC include targeted therapies and platinum-based doublet chemotherapy, paclitaxel and carboplatin or paclitaxel and carboplatin plus bevacizumab. Although immunotherapies targeting the PD-L1/PD-1 pathway are available for advanced NSCLC beyond the first line, chemotherapy is a key first-line option for patients, despite poor survival outcomes, highlighting the need for additional treatment options. Atezolizumab, a monoclonal anti–PD-L1 antibody, inhibits the binding of PD-L1 to its receptors PD-1 and B7-1, restoring tumor-specific T-cell immunity. Clinical efficacy has been reported with atezolizumab monotherapy in patients with squamous and nonsquamous NSCLC, with a survival benefit observed across all PD-L1 expression levels. Additionally, Phase Ib data showed the potential for chemotherapy to further enhance responses to atezolizumab, with tolerable safety, in patients with NSCLC. Bevacizumab in combination with atezolizumab may enhance efficacy in non-squamous NSCLC by inhibiting VEGF-mediated immunosuppression. Four global, Phase III, randomized, open-label trials are evaluating atezolizumab+platinum-based chemotherapy, bevacizumab in chemotherapy-naive patients with stage IV NSCLC Methods: Eligible patients must have stage IV NSCLC, measurable disease (RECIST v1.1) and ECOG PS 0-1 and be chemotherapy naive. Patients will be enrolled regardless of PD-L1 expression status. Patients randomized to the experimental arm will receive atezolizumab 1200 mg with standard platinum-based chemotherapy in IMPower130 and 131 and bevacizumab in IMPower150. In IMpower131, experimental arm patients will receive atezolizumab+platinum-based chemotherapy+metavuxetax, then maintenance with atezolizumab+bevacizumab. Patients receiving atezolizumab may continue for four or six 21-day cycles, then maintenance with atezolizumab in IMpower130 and 131 and atezolizumab+bevacizumab in IMPower150. In IMpower132, experimental arm patients will receive atezolizumab+platinum-based chemotherapy+metavuxetax, then maintenance with atezolizumab+bevacizumab. Patients receiving atezolizumab may continue until loss of clinical benefit. Co-primary endpoints are progression-free survival and overall survival. Secondary endpoints include objective response rate and safety. Evaluation of predictive biomarkers associated with efficacy will be performed.

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ECOG PS, Eastern Cooperative Oncology Group performance status; IHC, immunohistochemistry. Results: Section not applicable Conclusion: Section not applicable

Keywords: atezolizumab, Immunotherapy, NSCLC, clinical trials

Abstracts

POSTER SESSION 3 - P3.02C: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/IMMUNOTHERAPY

IT - WEDNESDAY, DECEMBER 7, 2016

**P3.02C-039 ENDOCRINOLOGICAL SIDE EFFECTS OF NIVOLUMAB IN ADVANCED NON-SMALL CELL LUNG CANCER**

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Background: Immune check-point inhibitors (ICPIs) are considered well-tolerated drugs. Previous experiences with ipilimumab or nivolumab in NSCLC patients have shown possible endocrine toxicities, while less data have been collected about Nivolumab. ICPIs act by blocking inhibitory signaling and, therefore, enhancing T-cell activity against tumor cells. This mechanism might result in impaired self-tolerance with subsequent development of immune-related adverse events (irAEs), and endocrine toxicities are especially relevant. Methods: From May 2015 to April 2016, 74% patients with advanced pretreated NSCLC (52 Male, 22 Female, mean age: 64 years) received at least one dose of nivolumab (3 mg/Kg every 14 days) within a single-istitutional translational research trial. Blood samples were collected at baseline and at each cycle in order to monitor hormone (TSH, ACTH, cortisol, Prolactin[PRL] and testosterone) serum levels and autoantibodies (ATG, ATPO and anti-TSH) formation. Thyroid morphology was evaluated by ultrasonography at baseline, eventually repeated if TSH anomaly was observed. Results: Thyroid function was assessed in all 74% patients. At baseline, 6 patients had impaired thyroid function: 5 with reduced TSH, including two undergone previous thyroidecction that required reduction in levothyroxine replacement therapy, and 1 with increased TSH. During treatment, 4 patients developed transient thyrotoxicosis evolving to hypothyroidism in 75% of cases. All patients with transient thyrotoxicosis reported increased thyroid autoantibodies; 8 patients developed hypothyroidism, with negative thyroid autoimmunity. Adrenocortical axis was evaluable in 55 subjects, of which 14 under steroid (equivalent of 10 mg of prednisone) therapy (one had partial hypopituitarism). Among the remaining 31 patients, 7 showed significant cortisol alterations (2 elevated, 5 reduced). Gonadal axis was evaluated in 73 male patients; among these, one was taking testosterone replacement therapy for partial hypopituitarism and one was receiving GnRH antagonists. No significant change on gonadal status was observed. PRL was assessed in 56 patients; among these, 10 were treated with drugs known to increase PRL levels; 20 patients had at least one elevated prolactin value, 7 from baseline and 13 developed during treatment. However, only 8 showed significantly increased values (>50 mcg/L in n=6, developed during treatment in 50% of cases; >100 mcg/L in n=2 from baseline). Conclusion: Thyroid function abnormalities, in particular non-autoimmune hypothyroidism and transient thyrotoxicosis on autoimmune basis, seem the major endocrine adverse event related to nivolumab. With respect to other hormonal axes, further conclusions might be drawn after a longer follow-up, due to the heterogeneity of available results and the presence of interfering factors.

Keywords: Nivolumab, Endocrinological toxicity, immunotherapy toxicity

**P3.02C-040 CHECKMATE 384: A PHASE 3B/4 DOSE-FREQUENCY OPTIMIZATION TRIAL OF NIVOLUMAB IN ADVANCED OR METASTATIC NON-SMALL CELL LUNG CANCER (NSCLC)**

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Background: Nivolumab, an anti-programmed death-1 antibody, is approved for previously treated metastatic NSCLC, advanced melanoma, advanced...
renal cell carcinoma (RCC), and relapsed/progressive classical Hodgkin lymphoma. In two phase 3 trials (CheckMate 017 and 057), nivolumab 3 mg/kg every 2 weeks (Q2W) demonstrated superior survival and favorable safety versus docetaxel in previously treated patients with metastatic NSCLC. Clinically meaningful efficacy and a manageable safety profile have been observed in studies in melanoma (CheckMate 037, 066, and 067), RCC (CheckMate 025), and Hodgkin lymphoma (CheckMate 205 and 039). On this basis, the currently approved nivolumab dose is 3 mg/kg Q2W. Decreasing the frequency of nivolumab administration may enhance convenience and compliance while maintaining efficacy and safety in patients who receive long-term nivolumab therapy. CheckMate 384 is a phase 3b/4 trial that will evaluate the efficacy and safety of nivolumab administered at two dosing frequencies in patients with advanced/metastatic NSCLC following ~4 months’ administration of nivolumab 3 mg/kg or 240 mg Q2W. Methods: Adult patients with advanced/metastatic squamous or nonsquamous NSCLC and ECOG performance status 0–2 are eligible; disease can be newly diagnosed or recurrent/progressive following multimodal therapy. Patients with untreated, symptomatic brain metastases are ineligible. Patients must have tolerated and completed ~4 months (16 ± 2 weeks) of treatment with nivolumab (3 mg/kg or 240 mg) Q2W and achieved a complete or partial response or stable disease. After this pre-study period, patients will be randomized 1:1 to receive iv nivolumab on one of two fixed-dose regimens: 240 mg Q2W or 480 mg Q4W. Randomization will be stratified by histology and response to pre-study nivolumab treatment at randomization (complete/ partial response vs stable disease). The table shows primary/secondary endpoints; the objective is to establish that nivolumab 480 mg Q4W is not inferior to 240 mg Q2W. Planned enrollment is 620 patients.

Primary Endpoints: Secondary Endpoints
Progression-free survival rate at 6 months after randomization: Progression-free survival rate at 1 year after randomization by tumor histology and by response before randomization
Progression-free survival rate at 1 year after randomization: Progression-free survival rate at 2 years after randomization
Overall survival rate (annually, up to 5 years after randomization): Safety and tolerability, as assessed by incidence and severity of adverse events

Results: Not applicable

Keywords: dosing frequency, Nivolumab, NSCLC, PD-L1

Poster Session 3 – P3.02C: Advanced NSCLC & Chemotherapy/Targeted Therapy

Wednesday, December 7, 2016

P3.02C-041 IMPower133: A PHASE I/II STUDY OF 1L ATezolizumAB WITh CARBOPlatin AND ETOPosIDE IN PATIENTS WITH EXTENSIVE-STAGE SCLC

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Background: For patients with advanced NSCLC without genetic driver alterations, cisplatin/carboplatin–pemetrexed is a standard-of-care first-line (1L) treatment for non-squamous histology; and cisplatin/ carboplatin–gemcitabine for squamous histology. Although immunotherapies targeting PD-L1/PD-1 are currently available for 2L+ NSCLC, chemotherapy remains the main 1L option for patients who require survival advantage. Atezolizumab, an anti–PD-L1 mAb, presents potential for improving quality of life in the 1L setting compared with current standard of care. The IMPower133 study is a randomized, open-label, phase 1/2 study of atezolizumab plus carboplatin and etoposide in treatment-naive patients with ES-SCLC. The study stratification factors include sex, ECOG performance status, and stage of disease. Patients with brain metastases are excluded.

Methods: Eligibility criteria include stage IV or recurrent/progressive disease following ≥1 systemic therapies, histologically confirmed ES-SCLC (squamous or non-squamous), Eastern Cooperative Oncology Group (ECOG) performance status 0–1, measurable disease, and adequate hematologic and renal function. Patients will be randomized 1:1 to receive atezolizumab 1200 mg IV Q2W and carboplatin (AUC 5 mg/mL/min IV, day 1) and etoposide (100 mg/m2, days 1–3) as initial therapy. A randomization window of 42 days will be allowed. In addition, patients can receive ≥1 prior chemotherapy if the latter regimen did not include cetuximab or erlotinib. Treatment cycles will continue until disease progression or unacceptable toxicity. The primary endpoint is confirmed objective response rate (ORR) per Response Evaluation Criteria In Solid Tumors (RECIST v1.1). Secondary endpoints include duration of response (DOR), time to progression (TTP), progression-free survival (PFS), overall survival (OS), and quality of life.

Results: In total, 111 patients have been treated with atezolizumab 1200 mg Q2W and carboplatin (AUC 5 mg/mL/min IV, day 1) and etoposide (100 mg/m2, days 1–3). Of these, 101 patients have been evaluated for response. The confirmed ORR was 6% (n = 4/17 [partial response]; DOR of 17 months). In addition, patients were still receiving treatment at the time of analysis. Atezolizumab plus carboplatin and etoposide has shown promising clinical activity in patients with ES-SCLC and tolerable safety profile. Overall, the safety profile was consistent with that of previous atezolizumab studies, and an acceptable toxicity profile was observed in this study. Notably, there were no new toxicities associated with the addition of etoposide. No treatment-related deaths occurred during the study.

Keywords: atezolizumab, Immunotherapy, SCLC, clinical trials

Poster Session 3 – P3.02C: Advanced NSCLC & Chemotherapy/Targeted Therapy/I mmunotherapy

Wednesday, December 7, 2016

P3.02C-042 IMPower110: PHASE III TRIAL COMPARING 1L ATezolizumAB WITh CHEMOTHERAPy IN PD-L1–SELECTED CHEMOTHERAPy-NAIVE NSCLC PATIENTS

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Background: For patients with advanced NSCLC without genetic driver alterations, cisplatin/carboplatin–pemetrexed is a standard-of-care first-line (1L) treatment for non-squamous histology; and cisplatin/ carboplatin–gemcitabine for squamous histology. Although immunotherapies targeting PD-L1/PD-1 are currently available for 2L+ NSCLC, chemotherapy remains the main 1L option for patients who require survival advantage. Atezolizumab, an anti–PD-L1 mAb, presents potential for improving quality of life in the 1L setting compared with current standard of care. The IMPower110 study is a global, phase III randomized, open-label, multicenter, open-label trial, will evaluate efficacy and safety of atezolizumab vs cisplatin/carboplatin–pemetrexed or gemcitabine as 1L therapy for PD-L1–selected chemotherapy-naive patients with advanced non-squamous or squamous NSCLC, respectively. Methods: Eligibility criteria include stage IV non-squamous or squamous NSCLC, measurable disease (RECIST v1.1), ECOG PS 0–1, no prior chemotherapy for advanced NSCLC and centrally-assessed PD-L1 expression ≥1% on TC or IC (TC1/2/3 or IC1/2/3 with VENTANA SP142 IHC assay; expected prevalence, >65%). Exclusion criteria include active or untreated CNS metastases, prior immune checkpoint blockade therapy or autoimmune disease. Patients will be randomized 1:1 to receive atezolizumab or cisplatin/carboplatin–pemetrexed (non-squamous) or gemcitabine (squamous) for 4 or 21-day cycles. Patients in comparator arms can receive pemetrexed (non-squamous)/best supportive care (squamous) until RECIST v1.1 disease progression. Patients receiving atezolizumab may continue until loss of clinical benefit. Co-primary endpoints are PFS and OS. Key secondary endpoints include ORR, DOR, IRF- assessed PFS (RECIST v1.1) and TTO. Safety and PK will also be evaluated. Tumor biopsies at RECIST v1.1 progression will be assessed for immunologic biomarkers associated with responses to atezolizumab and to differentiate non-conventional responses from radiographic progression.
**P3.02C-044 NIVOLUMAB-RESPONSE IN A PATIENT WITH ADVANCED SQAMOUS NSCLC OCCURRING SIMULTANEOUSLY WITH SIAD**

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Background: Nivolumab is a human IgG4 monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing the anti-tumor immune response. Due to the novelty of the mechanism of action and the limited treatment experience all checkpoint inhibitors can potentially induce treatment related AEs in any organ system that have not been noticed until now. The Syndrome of Inappropriate Diuresis (SIAD) leading to hyponatremia with variant symptoms of CNS affection is a frequent paraneoplastic syndrome in patients with advanced cancer, especially small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), but can also be induced by a large number of anticancer drugs, however, not reported for Nivolumab until now. Methods: We reported a 55-years old healthy pretreated patient who was first diagnosed with squamous NSCLC in 2012. After symtomatic progression he started 42nd line therapy on Nivolumab treatment (3mg/kg, q2w) in August 2015 after EMA licensing. Results: After 3 months of treatment we noted disease stabilization with a radiographic minor response together with a slight improvement of tumor symptoms. Thus, therapy was continued. After 6 months treatment CT scan showed for the first time a partial response, however patient reported a clinical deterioration with onset of new symptoms (headache, dizziness, fatigue, nausea, blurred vision). Lab results showed severe hyponatremia (nadir 116 mmol/l) caused by SIAD (serum osmolality 254 mOsm/kg), possibly induced by Nivolumab as other potential causes were excluded. No signs of intracranial progression or hypophysitis (brain MRI, CSF cytology, endocrinology lab) were detected. In the phase III registration trial the median time to response was 2.2 months. In our patient hyponatremia occurred in a timely relationship with partial response of the disease (after 6 months of treatment). After 2 months tolvaptan treatment (an oral ADH antagonist) sodium levels normalized, accompanied by improvement of hyponatremia-symptoms. The patient is still in PR on Nivolumab treatment without treatment interruptions with normal sodium levels. Conclusion: We report a patient case (squamous NSCLC) where Nivolumab was not able to induce long lasting radiographic remissions or clinical benefit. After switching to Nivolumab therapy the patient achieved a partial remission after 6 month of continuous Nivolumab with a simultaneous onset of hyponatremia. To the best of our knowledge, this is the first report of a Nivolumab response occurring simultaneously with SIAD. Therefore we speculate that hyponatremia might be a predictor for Nivolumab treatment response.

Keywords: Hyponatremia, Nivolumab, SIAD

**P3.02C-045 EXPERIENCE WITH NIVOLUMAB IN COMPASSIONATE USE IN NON-SMALL LUNG CARCINOMA PATIENTS WHO HAVE PROGRESSED TO ONE OR MORE PRIOR LINES OF CHEMOTHERAPY**

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Background: Treatment options for patients with stage IIIB and IV NSCLC who progressed to one or more prior lines of chemotherapy are limited. Immunotherapy represents a promising alternative for NSCLC patients. The aim of our study is to analyze nivolumab in compassionate use in our centre. Methods: A retrospective study of patients with stage IIIB and IV NSCLC who progress to chemotherapy and receive Nivolumab in compassionate use. A descriptive analysis using chi-square test and survival analysis using Kaplan-Meier estimates. The radiological response was assessed by RECIST 1.1 and immune-related adverse effects (irAEs). Results: Thirty-two patients were included between July 2015 and March 2016. 87.5% men, 12.5% women, 75% adenocarcinoma and 25% squamous, from which 71% received nivolumab in second line and 29 % in third line or more; 12.5 % had PS 2 and 25 % brain metastases. The response rate...
observed was 17.4% in the second line and 20% in third line or more, with a progression-free survival (PFS) of 4 months (95% CI: 2.3-5.4) and 10 months (95% CI: 2.9-18), respectively. The average number of administered cycles was 6 ± 1 in PS2 and 18 when there was pseudoprogression (n = 5). The observed iRAEs were: grade GI 11 (34%), GI 4 (12%) and GI 5 (3%), 6% pneumonitis (with previous radiotherapy), 3% autoimmune hepatopathy, 3% pemphigoid and 3% hypothyroidism. Global survival (GS) in PS50 was 6.5 months (95% CI: 4.6-8.3), PS51 of 7.4 (95% CI: 6.8-8.7) and PS2 of 1 (95% CI: 0.6-7.0), with p<0.001. The GS with an Erlotinib PO QD was 3 months (95% CI: 1.7-4.2) vs. 7.9 months (95% CI 9.6-8.7), with p>0.001, in patients without brain metastasis. Conclusion: In our series, nivolumab was well tolerated and demonstrated clinical benefit both in second and in third line, except in patients with PS2 and/or brain metastases. Patients that present pseudoprogression obtain major benefit and more occurrence of incidence of iRAEs (possible indicator of response). External validity is limited by the small number of patients and this is not a randomized study.

Keywords: compassionate, Nivolumab, non-small lung cancer, chemotherapy

P3.02C-046 SAFETY, CLINICAL ACTIVITY AND BIOMARKER RESULTS FROM A PHASE IB STUDY OF ERLOTINIB PLUS ATEZOLIZUMAB IN ADVANCED NSCLC

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Background: Targeted therapy with erlotinib is effective in reducing tumor burden in EGFR-mutant non-small cell lung cancer (NSCLC). However, resistance to therapy develops almost universally. Atezolizumab, an engineered mAb that inhibits binding of PD-L1 to its receptors, PD-1 and B7, has demonstrated promising monotherapy activity in NSCLC. Given that atezolizumab may enhance and perpetuate anti-tumor immunity, we hypothesized that combining atezolizumab with erlotinib may improve both clinical response and durability in EGFR-mutant NSCLC. Methods: This Phase Ib study consisted of a safety-evaluation stage in patients with NSCLC regardless of EGFR status followed by an expansion stage in TKI-naive patients with tumors harboring activating EGFR mutations. Patients were enrolled following a 2-4 week run-in with erlotinib PO QD alone, patients received 150mg erlotinib PO QD and 1200mg atezolizumab IV q3w. To evaluate immune biology, biopsies were obtained in expansion-stage patients pre-treatment, after erlotinib run-in, at weeks 4-6, and at progression. The primary objective was to evaluate the safety and tolerability of the combination. Secondary objectives included evaluation of the clinical activity per RECIST v1.1. Data cutoff, 11 April 2016. Results: Twenty-eight patients (safety stage, n = 8; expansion stage, n = 20) who received ≥1 dose of erlotinib or atezolizumab were considered safety evaluable. Median age was 69y (range, 47-84); median survival follow-up was 11.2mo (range, 1.6-14.7). Sixty-two percent had received 2 or more prior chemotherapy regimens. At baseline, 40% had >3 liver metastases. The ORR for the combination was 75% (95% CI, 51-91). Disease control rate (CR + PR + SD ≥ 6: 1 in PS2 and 18 when there was pseudoprogression (n=5) with 100% ORR had at least 1 adverse event, the most common being anemia (9 patients). Only 1 (3%) grade 3 event was documented. Conclusion: Nivolumab was well tolerated and led to disease control in 48% of patients in this early analysis, after a short follow-up. Survival data will be updated for presentation.

Keywords: immunotherapy, nivolumab, lung cancer, survival.

P3.02C-047 LOCAL EXPERIENCE IN AN EXPANDED ACCESS PROGRAM OF NIVOLUMAB IN ADVANCED NON-SMALL CELL LUNG CANCER IN BRAZIL

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Background: Nivolumab is a new standard-of-care in platinum-refractory Non-small cell lung cancer (NSCLC), with significant survival increment in comparison to docetaxel shown in two phase 3 trials. Herein, we report the local experience in an expanded access program in Brazil. Methods: Patients with recurrent or metastatic NSCLC, treated with at least one prior chemotherapy regimen, were potentially eligible. Overall, three hundred twenty-two patients were screened in the country, and 287 were enrolled. Around 10% of these (N=29) were treated in a single cancer institution in Rio de Janeiro. The aim is to describe the early outcome in these 29 patients. Results: Median age was 64 years (range 37-83), most patients were male (62%), white (66%), smoker or former smoker (21% and 55%, respectively). Most cases (59%) were classified as non-squamous, and only 3 had a documented EGFR mutation. Sixty-two percent had received 2 or more previous chemotherapy lines. After a median follow-up of 4.9 months (95% CI, 4-2.5-5), 1 partial response (3%) was documented, and 13 patients (45%) presented with disease stabilization by RECIST 1.1. Median PFS and OS were not reached, and 6-month OS was 52%. Seventeen patients (59%) had at least 1 adverse event, the most common being anemia (9 patients). Only 1 (3%) grade 3 event was documented. Conclusion: Nivolumab was well tolerated and led to disease control in 48% of patients in this early analysis, after a short follow-up. Survival data will be updated for presentation.

Keywords: immunotherapy, nivolumab, lung cancer, survival.
(22%) developed grade 3 treatment-related toxicity (2 colitis, hepatitis, pneumonitis, hypothyroidism, conjunctivitis). In the SBRT and post-SBRT phases, there have been no grade 2 or greater treatment-related events.

Conclusion: The addition of SBRT to pembrolizumab monotherapy underwent SBRT and now have irSD, with some evidence of tumor regression. Updated results will be presented.

Keywords: immune checkpoint inhibitor, abscopal, SBRT, radiation

P3.02C-049 DENDRITIC CELLS MODIFIED WITH TUMOR-ASSOCIATED ANTIGEN GENE DEMONSTRATE ENHANCED ANTITUMOR EFFECT AGAINST LUNG CANCER
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Background: Immunotherapy involving dendritic cells (DCs) vaccine has the potential to overcome the bottleneck of cancer therapy. Methods: Here, we engineered Lewis Lung cancer cells (LLC) and bone marrow derived DCs to express tumor-associated antigen (TAA), ovalbumin (OVA) via lentiviral vector plasmid encoding OVA gene. We then tested the anti-tumor effect of modified DCs both in vitro and in vivo. Results: The results demonstrated that in vitro modified DCs could dramatically enhance T cells proliferation (P < 0.01) and kill LLC significantly than control groups (P < 0.05). Moreover, modified DCs can reduce tumor size and prolong the survival of tumor-bearing mice than control groups (P < 0.01, P < 0.05; respectively). Modified DCs also enhanced homing to T-cell rich compartments and triggered naive T cells to become cytotoxic T lymphocytes, which exhibited significant infiltration into the tumors. Interestingly, modified DCs also markedly reduced tumor cells harboring stem cell markers in mice (P < 0.05), suggesting the potential role of eliminating cancer stem-like cells in vivo.

Conclusion: These findings indicated that DCs bioengineered with TAA may enhance antitumor effect against murine lung cancer through novel mechanism that is worth further exploration.

Keywords: dendritic cell, cancer stem-like cell, immunotherapy, lung cancer

P3.02C-050 IMPOWER010: PHASE III STUDY OF ATEZOZILUMAB VS BSC AFTER ADJUVANT CHEMOTHERAPY IN PATIENTS WITH COMPLETELY RESECTED NSCLC
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Background: Early-stage non-small cell lung cancer (NSCLC) is treated surgically, but 30%-70% of patients experience post-resection recurrence and succumb to disease. Adjuvant chemotherapy is the standard of care for fully resected NSCLC (stages IB [tumors >2 cm]-IIIA), and although cisplatin-based chemotherapy provides some benefit, the 5-year survival benefit is ≈5%, underscoring the unmet need. Atezolizumab is an anti-PD-L1 monoclonal antibody that inhibits PD-L1 from binding to its receptors PD-1 and B7-1, thereby restoring anti-tumor immune response. Atezolizumab monotherapy has demonstrated promising efficacy and tolerable safety in patients with previously untreated advanced NSCLC, with a survival benefit observed across all PD-L1 expression levels. Given the need to improve survival for patients with early-stage NSCLC, IMPower010 (NCT02486718), a global Phase III randomized, open-label trial, has been initiated to compare the efficacy and safety of atezolizumab with best supportive care (BSC), following adjuvant cisplatin-based chemotherapy in patients with resected stage IB (tumors >2 cm)-IIIA NSCLC. Patients must have adequately recovered from surgery, be eligible to receive cisplatin-based adjuvant chemotherapy and have an ECOG PS 0-1. Exclusion criteria include the presence of other malignancies, use of hormonal cancer or radiation therapy within 5 years, prior chemotherapy, autoimmune disease or exposure to prior immunotherapy. Approximately 1127 patients, regardless of PD-L1 expression status, will be enrolled. Eligible patients will receive up to 21-27 cycles of cisplatin-based chemotherapy (cisplatin [75 mg/m² IV day 1] + either vinorelbine [30 mg/m² IV days 1, 8], docetaxel [75 mg/m² IV day 1] or gemcitabine [1250 mg/m² IV days 1, 8], or pemetrexed [500 mg/m² IV day 1; non-squamous NSCLC only]). Adjuvant radiation therapy is not permitted. Following adjuvant treatment, eligible patients will be randomized 1:1 to receive atezolizumab (1200 mg every 16 cycles) or BSC. Stratification factors will include sex, histology (squamous vs non-squamous), extent of disease (stage IB vs II vs IIIA) and PD-L1 expression by IHC (TC, tumor cell; IC, tumor-infiltrating immune cell; TC2/3 [>5% expressing PD-L1] and any IC vs TC0/1 [<5%] and IC2/3 [>5%] vs TC0/tand IC0/1 [<5%]). The primary endpoint is disease-free survival, and secondary endpoints include overall survival and safety. Exploratory endpoints include PD-L1 status, immune and tumor related biomarkers before, during and after treatment with atezolizumab and at radiographic disease occurrence or confirmation of new primary NSCLC. Results: Section not applicable Conclusion: Section not applicable

Keywords: clinical trials, atezolizumab, Immunotherapy, NSCLC

P3.02C-051 A PRE-TREATMENT SERUM TEST BASED ON COMPLEMENT AND IL-10 PATHWAYS IDENTIFIES PATIENTS BENEFITING FROM THE ADDITION OF BAVITUXIMAB TO DOCETAXEL
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Background: SUNRISE, a global, double-blind, Phase III trial of docetaxel (D) plus bavituximab (B) or D plus placebo (P) in previously treated non-squamous non-small cell lung cancer, demonstrated similar overall survival (OS) in both treatment arms. Mass spectrometry and correlational analysis were used to create a test able to identify a subgroup of patients benefitting from the addition of B to D. Methods: Pre-treatment serum samples were available for 197 of the first 200 subjects enrolled in the trial. Mass spectra could be generated for 193 samples using the Deep MALDI method (Duncan et al, ASMS 2013), processed and features (peaks) identified. Mass spectral (MS) features associated with various biological functions were identified using a gene set enrichment analysis approach. Analysis of scores based on these MS feature subsets indicated that in patients with high complement activation outcome depended on IL10 interaction in D+B but not in D+P. A test using the MS features associated with these functions was created to reliably identify a patient subgroup associated with clinical benefit using modern machine learning methods. Results: Complement activation, as assessed by the classifier trained using related MS features, was a prognostic factor in both treatment arms, with high activation associated with poorer clinical outcome (OS HR = 0.54, log-rank p = 0.013 for D+B; OS HR = 0.60, log-rank p = 0.040 for D+P). Within the subgroup with high complement activation (N=50 (D+B);
N=54 (D+P), a second classifier using features related to IL-10 activation was able to isolate a subgroup of patients showing numerical benefit from the addition of B (median OS 5.9 months (D+P), 12.5 months (D+B)). The remaining subgroup showed no benefit from addition of B (median OS 10.4 months (D+P), 5.6 months (D+B)). Blinded validation of the test in the remainder 397 patients randomized in SUNRISE is will be presented. Conclusion: Proteomic and correlative approaches identified complement activation and low IL-10 levels as important pathways for predicting improved outcomes of patient treatment with D+B, in line with preclinical work on B’s mechanism of action. The test resulting from this work will undergo blinded independent validation.

P3.02C-052 ELECTRONIC NOSE: AN EARLY RESPONSE BIOMARKER FOR ANTI-PD1 THERAPY IN PATIENTS WITH NSCLC

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Background: Multiple studies have shown the activity of the anti-PD(L)-1 agents in patients with advanced non-small-cell lung cancer (NSCLC). There is an urgent need to explore biomarkers that predict outcome to anti-PD-1 therapy. The electronic (e) Nose is used to analyse the exhaled gasses and is under development as a diagnostic tool for lung cancer. We aimed to determine the diagnostic accuracy of exhaled breath analysis for responders vs. non-responders to anti-PD-1 treatment in NSCLC patients. Methods: Patients with NSCLC who were about to receive Nivolumab, were asked to participate. At baseline and after 6 weeks of treatment exhaled breath analysis took place. Breathprints were collected in duplicate by an e-Nose positioned at the rear end of a pneumotachograph (SpiroNose) (de Vries J Breath Res 2015). REGIST.1.1 criteria were used for response evaluation at three months and six months and reported accordingly: Complete response (CR), Partial response (PR), stable disease (SD), and progressive disease (PD). Data-analysis involved signal processing, environment correction and statistics based on principal component analysis (PCA), followed by discriminant analysis (Matlab2014/SPSS20). Results: From August 2015 until April 2016, 56 patients participated in this trial. Forty-two patients had a response evaluation. Principal component 3 and 4 showed a significant difference (p<0.005 and p<0.001) between responders (PR and SD) and non-responders (PD) [Figure A]. Twenty five patients had a second exhaled breath analysis after 6 weeks. Analysis showed significant differences in PC3 and PC4 between both SD vs. PR (p<0.001) and PD vs. PR (p<0.002) [Figure B].

Conclusion: E-Nose is able to discriminate between responders and non-responders to anti-PD1 therapy at baseline and 6 weeks follow-up and may therefore be of great value to predict outcome.

Keywords: Non-small cell lung carcinoma, Immunotherapy, Predictive biomarker

P3.02C-053 CLINICAL AND PLASMA BIOMARKERS FOR DISEASE CONTROL WITH NIVOLUMAB TREATMENT FOR ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC)

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Background: Anti-PD1 antibodies have become the treatment of choice for most advanced NSCLC patients after failure of first line platinum-based chemotherapy. Responses are seen in roughly 20% of treated patients. PD1 expression level and mutational burden might be predictive factors but are not always available and their predictive accuracy is limited. Predictive biomarkers are urgently needed. We hypothesized that clinical data and baseline blood tests might be predictive for benefit from nivolumab.

Methods: A chart review was performed of patients with advanced NSCLC who received at least one cycle of nivolumab, at one of three cancer centers during 2015-2016. Additional inclusion criteria were: available baseline clinical data, evaluation of response and availability of blood test results. Blood test results collected were: Absolute Lymphocyte Count (ALC), Absolute Neutrophil Count (ANC), White Blood Cells (WBC), Hemoglobin (Hb), Platelets (PLT), Albumin (ALB), Lactate Dehydrogenase (LDH). Blood test results were collected at baseline and before the second and third treatment. Disease control (DC) was defined as any tumor shrinkage, or stable disease for at least 6 months, as assessed by the treating physician by computerized tomography scans. Patients with DC were compared with patients with progressive disease (PD, patients progressing within the first 6 months). Uni- and multivariate regression analyses were performed using Stata (version 11.2, StataCorp). Results: A total of 79 patients treated with nivolumab were included, median age 67 years, 66% males, 27% with DC. DC patients compared to PD patients were younger (61.6 vs 69.3 yr, p<0.001), more females (42% vs 27%, p<0.05), and had a lower baseline WBC (6.9 vs 9.2 K/µl, p<0.05). The difference in WBC between DC and PD patients increased during treatment (2.3 K/µl at baseline, 2.6 prior to third treatment). Lower baseline neutrophil count was associated with DC (p=0.02). Neither performance status nor LDH predicted outcome on uni-variante analysis. On multivariate analysis age (p=0.050) and baseline WBC (p=0.02) were associated with outcome. Patients less than 67 years of age with baseline WBC>8.04 K/µl (n=118) had DC rate of 56%, while DC rate was 4% in patients 67 years or more, with WBC>8.04 K/µl (n=23).

Conclusion: We have identified clinical biomarkers (age and baseline WBC) that are associated with DC under nivolumab treatment. Validation on an independent data set is warranted. The association of a low peripheral WBC with improved response rate raises the possibility that acute inflammatory responses are counteractive to anti-PD1 therapy.

Keywords: Nivolumab, Biomarkers, response, NSCLC

P3.02C-054 PROGNOSTIC ROLE OF CFDNA IN PATIENTS WITH NSCLC UNDER TREATMENT WITH NIVOLUMAB

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Background: Nivolumab is a programmed death-1 (PD-1) immune checkpoint inhibitor approved for previously treated advanced non-small cell lung cancer (NSCLC). Liquid biopsy is a non-invasive blood test that detects cell-free DNA (cfDNA) shed from the tumour into the bloodstream. Monitoring cfDNA in patients with NSCLC under treatment with Nivolumab may be helpful to assess efficacy of the therapy and may be related with patients’ survival.

Methods: Peripheral blood samples were obtained from 74 patients with pretreated advanced NSCLC within a single-institutional translational research trial from May 2015 to April 2016. Patients received intravenous Nivolumab at 3 mg/kg every 2 weeks until progression or unacceptable toxicity. All the patients underwent CT-scan every 4 cycles and responses
were classified according to immune related Response Criteria. cfDNA was extracted from plasma using the Circulating Nucleic Acid Kit (Qiagen). The quantification of cfDNA (ng/ml plasma) was performed by qPCR using H-ErT single copy gene. Kaplan-Meier survival function was used to compare survival curves from cfDNA at baseline and at the time of first evaluation (after 4 cycles of Nivolumab). Results: Among the 74 enrolled patients 72 were evaluable for cfDNA survival analyses; 14 experienced early death, 25 progressive disease (PD), nine partial response (PR), 19 stable disease (SD) and five were not evaluable for response. 27 out of the 28 responsive patients (PR+SD) are still alive at the time of analysis. In 25 evaluable patients with PD after the first radiological evaluation, median cfDNA < 786 ng/ml was significantly associated with an improved median survival as compared to cfDNA ≥ 786 ng/ml (295 vs 96 days respectively, HR=0.09290, 95% CI 0.019987-0.4332, p-value: 0.00023; similar results have been obtained in the subset of 25 patients progressing at best response (p-value: 0.0042). Analyzing the OS of the 72 evaluable patients, median survival of those with cfDNA < 786 ng/ml (25 vs 96 days respectively, HR=0.09290, 95% CI 0.019987-0.4332, p-value: 0.00023) was still undetermined, while it is equal to 181 days for those with cfDNA ≥ 786 ng/ml (HR 0.1674-0.7568, p-value 0.0035). Conclusion: Our preliminary data show a significantly improved survival for NSCLC patients with cfDNA < 786 ng/ml (HR 0.3559, 95%CI 0.1674-0.7568, p-value 0.0035). Conclusion: Our preliminary data show a significantly improved survival for NSCLC patients treated with Nivolumab having cfDNA < 786 ng/ml than those with higher cfDNA; the correlation with OS is observed in patients at the first radiological evaluation and in those with PD at best response.

Keywords: cfDNA, Nivolumab, liquid biopsy, non-small cell lung cancer

Poster Session 3 – P3.02C - Advanced NSCLC & Chemotherapy/Targeted Therapy/Immunotherapy
It – Wednesday, December 7, 2016

P3.02C-055 INCREASED INCIDENCE OF IMMUNE-RELATED PNEUMONITIS IN ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC) PATIENTS TREATED WITH ANTI-PD1 ANTI-BODIES
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Background: Advanced non-small cell lung cancers (NSCLC) can be treated with anti-PD1 (programmed death 1) antibodies. Anti-PD1 therapy can lead to immune mediated adverse events. This study examines the incidence of pneumonitis, a potentially fatal complication, in patients with advanced NSCLC treated with anti-PD1 antibodies at 3 large hospitals in Sydney, Australia. Methods: NSCLC patients commenced on pembrolizumab (2 mg/kg or 10 mg/kg Q3W) or nivolumab (3 mg/kg Q2W) were assessed for adverse events including pneumonitis. Patient demographics, treatment history and immune mediated complications were collected. Pneumonitis was graded according to the Common Terminology Criteria for Adverse Events Version 4.0. Pneumonitis treatment and clinical outcomes were collected. Serial imaging was reviewed with a blinded radiologist. Results: A total of 104 patients between 2012 and 2016 were treated with anti-PD1 therapy. Median age for included patients was 67. Forty-four (14%), 35 (34%), and 53 (51%) had anti-PD1 as first, second, or third and subsequent line treatment respectively. Nine patients (9%) developed pneumonitis. Three patients (4%) developed grade 3 (G3) or higher pneumonitis including one patient (1%) that died due to pneumonitis. All patients with ≥ G3 pneumonitis required hospital admission with one requiring admission to a high dependency unit. None of the patients with ≥ G3 pneumonitis were retreated with anti-PD1 therapy. All patients with ≥ G3 pneumonitis died within 5 weeks of their diagnosis of pneumonitis. Seven patients with pneumonitis were treated with steroids. The median length of treatment with steroid was 29 days. Pneumonitis involved both lungs in 3 patients. Of the remaining 6 patients – 2 had all right lung lobes involved, 2 had two lobes and 1 had one lobe. Fifteen (14%) patients had a history of receiving concurrent chemoradiotherapy prior to anti-PD1 therapy. A further 6 (6%) had curative intent radiotherapy and 3 (3%) had palliative radiotherapy to the thorax prior to anti-PD1 therapy. One of the patient with G3 pneumonitis had previously received radiotherapy to the chest. No association between prior radiotherapy and pneumonitis was seen. Conclusion: The incidence of pneumonitis is rare but our real-life multi-institutional data demonstrates a clinical incidence higher than reported in the literature. This complication can be life threatening and onset of ≥ G3 pneumonitis is associated with short survival.

Keywords: Radiotherapy, pneumonitis, PD-1, NSCLC

Poster Session 3 – P3.02C - Advanced NSCLC & Chemotherapy/Targeted Therapy/Immunotherapy
It – Wednesday, December 7, 2016

P3.02C-056 INTERIM RESULTS FROM THE PHASE I STUDY OF NIVOLUMAB + NAB-PACLITAXEL + CARBOPLATIN IN NON-SMALL CELL LUNG CANCER (NSCLC)
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Background: Chemotherapy, including nab-paclitaxel, plus an immune checkpoint inhibitor has demonstrated antitumor activity in patients with metastatic breast cancer (MBC) and NSCLC. Here, results from the 2 lung cohorts of the phase I nivolumab + nab-paclitaxel in pancreatic cancer (± gemcitabine), NSCLC (± carboptatin), and MBC safety trial are presented. Methods: Enrollment in the lung cohorts (C and D) was initiated in two sequential parts: Dose-limiting toxicity (DLT) evaluation was done in Part 1 prior to treatment arm expansion in Part 2. Chemotherapy-naive patients with stage IIIIB/IV NSCLC received 4 cycles of nab-paclitaxel 100 mg/m² D 1, 8, 15 + carboptatin area under the curve (AUC) 6 D 1 + nivolumab 5 mg/kg D 15 (starting in cycle 1 [Arm C] or cycle 3 [Arm D]) of each 21-day cycle. nab-paclitaxel continued as monotherapy from cycle 5. Primary endpoints were DLTs (Part 1), and grade 3/4 treatment-emergent adverse events (TEAEs) and TEAEs leading to discontinuation (Parts 1 and 2). Patients who received ≥ 2 nab-paclitaxel cycles and remained on study for 14 days after the last nab-paclitaxel dose or discontinued due to DLT prior to completing 2 nab-paclitaxel cycles were considered DLT evaluable. Key secondary endpoints include safety, PFS, OS, and ORR. Results: As of May 25, 2016, 21 patients have enrolled in Arm C (18 nivolumab-treated; most were aged ≥ 65 years (57%) and female (71.4%), 33.3% had ECOG PS 0, 42.9% and 33.3% had adenocarcinoma and squamous cell carcinoma, respectively. No DLTs were reported (5 DLT-evaluable patients). The most common grade 3/4 AEs in Arm C (all patients) were neutropenia (26.8%), anemia (19.0%), and hypokalemia (14.3%); gastrointestinal disorders (11.1%) were the most frequent grade 3/4 immune-related AE in nivolumab-treated pts. Seven patients (5 nivolumab-treated) discontinued treatment (majority due to progressive disease [PD]). Of the 18 nivolumab-treated patients, 9 had a PR, 8 had stable disease, and data is pending in 1 patient; tumor shrinkage (baseline to nadir) ranged from 3% to 83%. The median PFS (n = 4 with PD or death; nivolumab-treated) was 7.3 months (treatment duration, 0.7 - 9.4 months). Eight patients have enrolled in Arm D (n = 2 with PD; nivolumab-treated). DLT pneumonitis was reported in 4 DLT-evaluable patients. Conclusion: These results demonstrate that the combination of nivolumab with nab-paclitaxel/carboptatin is tolerable and has promising antitumor activity in patients with NSCLC. Updated results will be presented at the meeting. (NCT02309177)

Keywords: Nivolumab, nab-paclitaxel, carboptatin, non-small cell lung cancer

Poster Session 3 – P3.02C - Advanced NSCLC & Chemotherapy/Targeted Therapy/Immunotherapy
It – Wednesday, December 7, 2016

P3.02C-057 VIROIMMUNOTHERAPY WITH VESICULAR STOMATITIS VIRUS EXPRESSING INTERFERON-β (VSV-IFNβ) IN A MURINE MODEL OF NSCLC
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Background: VSV-IFNβ is a live, replicating oncolytic virus with activity against NSCLC. We have previously shown that VSV-IFNβ leads to an inflamed tumor microenvironment and enhances anti-tumor immunity in a syngeneic mouse model. Furthermore, we have observed increased DLD1 expression on tumor cells after intratumoral injection with VSV-IFNβ. Here, we have further explored the mechanisms by which VSV-IFNβ exerts its immunologic effects and combined therapy with anti-PD1 and anti-PDL1 antibodies. Methods: VSV-human and murine IFN-β (hIFNβ and mIFNβ), respectively and VSV-IFNβ-NIS are manufactured by the Imaris Life (Rochester, MN) and

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Background: Inhibitors of PD1/PD-L1 checkpoint have been shown to be active in a broad range of cancers including non-small cell lung cancer (NSCLC). They induce proliferation of T cells within the tumor microenvironment (as revealed by IHC) leading to tumor eradication. There is however lack of detailed molecular characterization of T cells within the tumor microenvironment. CD8 T cell depletion experiments and combination treatments with checkpoint blockade for NSCLC.

Methods: We performed next-generation T cell receptor alpha/beta chain sequencing on serially obtained tumor and PBMC samples from 54 NSCLC patients undergoing anti-PD1 therapy. We also performed clonal expansion experiments and antigen specificity analysis by IFNγ ELISPOT and intracellular cytokine staining. We identified concordant early clonal responders within unsorted PBMC and in CD8 positive/negative T cells. We also confirmed these expanded T cell clones to be CD8 positive and serve as a foundation for the development of novel treatment strategies for non-responders.

Results: We identified early clonal expansion of T cells within the tumor microenvironment (revealed by IHC) leading to tumor eradication. There is however lack of detailed molecular characterization of these proliferating T cells including the dynamics of their clonality during treatment and their correlation with response, their antigen specificity and the molecular mechanisms induced in the expanded clones at single cell level. Such understanding will serve as a biomarker to detect early response after one treatment cycle.

Conclusion: Our results showed that early clonal expansion of a defined population of CD8+ T cells detected both within the tumor and PBMC correlate with response to therapy. We also confirmed that the persistence of these unique T cells clones several months after their initial expansion correlates with durable response.

Keywords: Immunotherapy, biomarker, non-small cell lung cancer
was performed to detect PD-L1 and CD8 expression in NSCLC. The Kaplan–Meier (KM) survival curve was used to estimate disease-free survival (DFS) and overall survival (OS). Gene Set Enrichment Analysis (GSEA) was used to determine potentially relevant gene expression signatures. Results: 288 cases with stage I/IIA NSCLC were evaluated for PD-L1 and CD8+ TIL staining. Dual positive PD-L1 and CD8 (PD-L1+/CD8+) represents a predominant subtype in NSCLC, accounting for 36.5% (105/288), followed by PD-L1-/CD8- (24.3%, 70/288), PD-L1+/CD8+ (26.0%, 75/288) and PD-L1-/CD8- (13.2%, 38/288). Survival analysis of DFS (p = 0.031) and OS (p = 0.002) showed a significant difference between four subgroups. Furthermore, we analyzed the correlation between expression types of PD-L1/CD8 and mutation burden and antigent presentation. We can identify dual positive PD-L1 and CD8 was significant with increased mutation burden (p < 0.001), high frequency of mismatch repair (MMR) related gene mutation. More interestingly, tumor with dual positive PD-L1 and CD8 manifested a remarkable activated antigent presentation and T cell receptor signature compared with other subgroups.

Conclusion: Dual positive PD-L1 and CD8 was identified as a predominant subtype in NSCLC and correlates with increased immunogenicity. These findings provide the evidence that combined analysis of PD-L1 and CD8 in NSCLC may be a promising way to predict PD-1 blockade immunotherapy.

Keywords: PD-L1, Immunotherapy, NSCLC, CD8+ TIL

P3.02C-061 NEUTROPHIL/LYMPHOCYTE RATIO PREDICTS THE EFFICACY OF ANTI-PD-1 ANTIBODY IN PATIENTS WITH ADVANCED LUNG CANCER
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Background: Therapeutic antibodies to programmed death receptor 1 (PD-1) have shown clinical activity in lung cancer. The aim of this study is to investigate the clinical factors, including inflammatory markers such as neutrophil/lymphocyte ratio (NLR), to predict response to anti-PD-1 antibody in advanced lung cancer patients. Methods: We retrospectively analyzed 51 patients who had advanced lung cancer and had been treated with anti-PD-1 antibodies between 2013 and 2015. The values of NLR were assessed at two time points: at baseline (pre-treatment) and at 6 weeks after the start of treatment (post-treatment). NLR of 5 was used as the cutoff value. Results: The median age of the patients was 68 years; 76.5% were male, and 27.5% were never smokers. Most patients had adenocarcinoma (n = 28); 17 had squamous cell carcinoma, and 6 had others. Eighteen of 51 patients (35.3%) had clinical objective response to anti-PD-1 antibody. Non-adenocarcinoma histology and low post-treatment NLR was significantly associated with clinical response, while gender, smoking history, line of treatment and pre-treatment NLR were not predictive of response. Liver metastasis, brain metastasis, and high post-treatment NLR were significantly associated with worse tumor response. Patients with a high post-treatment NLR had significantly shorter PFS (median 1.3 months vs. 6.1 months, p < 0.001). Multivariable analysis demonstrated that high post-treatment NLR (hazard ratio [HR] 20.1, 95% confidence interval [CI] 5.5–73.9, p < 0.001), presence of liver metastasis (HR 5.5, 95% CI 2.1–14.6, p = 0.001), and CNS metastasis (HR 2.9, 95% CI 1.1–7.4, p = 0.027) were independent predictive factors for short PFS.

Conclusion: Clinical factors including post-treatment NLR at 6 week might be predictive of clinical benefits from anti-PD-1 antibody therapy in lung cancer.

Keywords: advanced lung cancer, Immunotherapy, Neutrophil/lymphocyte ratio, predictive factor

P3.02C-062 ANTI-LUNG CANCER EFFECT OF CD8+ T CELLS TRANSDUCED RETROVECTOR VECTOR ENCODING WT1-SPECIFIC TCRS AND SIRNAS TARGETING ENDOGENOUS TCRS
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Background: Using of genetically engineered T lymphocytes with tumor antigen-specific T-cell receptor for treatment of cancer has clinically proved promise, however, this approach is complicated by several potential problems: (1) on-target adverse events directed against normal tissues, especially when affinity-enhanced TCRs are used; (2) issues related to chain mispairing between the introduced TCR genes; (3) off-target adverse events because of inherent cross-reactivity of the introduced TCR. In this study, we examined in detail the efficacy and safety of normal CD8+ T lymphocytes transduced retroviral vector encoding siRNAs which specifically down-regulate endogenous TCR expression, and a siRNA-resistant WT1-specific TCR construct for adaptive immunotherapy against human lung cancer cells. Methods: A novel TCR vector system which simultaneously delivers shRNAs for endogenous TCR α/β genes and WT1-specific TCRs genes was transduced into normal peripheral CD8+ T cells. The safety and effectiveness of these transfectant against lung cancer cells was evaluated both in vitro and in vivo. Results: First, we confirmed the augmented and inhibitory efficacies of the WT1-specific TCRs with siRNAs targeting endogenous TCRs (WT1-iTCR) vector for expression of the respectively introduced and endogenous TCRs. The result indicating that sufficient functional suppression of endogenous TCR and enhanced expression of the introduced TCR are achievable using the WT1-iTCR vector. Secondly, The WT1-specific TCRs with siRNAs targeting endogenous TCRs double gene modified T cells were augmented cytotoxic activities compared with only WT1-TCR–transduced T cells against lung cancer cells by standard 5-hour 51Cr-release assays at various effector/target (E/T) ratios. Conclusion: These data revealed that WT1-iTCR vector system shows safety resulting from stronger expression of the introduced WT1-specific TCR with inhibition of endogenous TCRs. Results from this study also demonstrate that significant enhancement of anti-lung cancer cells reactivity of these WT1-iTCR gene-modified T cells. In summary, the present study shows considerable promise in terms of safety and efficacy for adoptive immunotherapy against lung cancer cells using WT1-specific TCRs with siRNAs targeting endogenous TCRs gene-engineered T cells.

Conclusion: Dual positive PD-L1 and CD8 was identified as a predominant subtype in NSCLC and correlates with increased immunogenicity. These findings provide the evidence that combined analysis of PD-L1 and CD8 in NSCLC may be a promising way to predict PD-1 blockade immunotherapy.

Keywords: PD-L1, Immunotherapy, NSCLC, CD8+ TIL
Keywords: T cell receptor gene, adaptive T-cell therapy, lung cancer, Immunotherapy

P3.02C-063 LACTATE DEHYDROGENASE (LDH) AS A SURROGATE BIOMARKER TO CHECKPOINT-INHIBITORS FOR PATIENT WITH ADVANCED NON–SMALL-CELL LUNG CANCER (NSCLC)
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Background: Effectiveness of immunotherapy has been observed in around 20% of cases, nowadays there is no accurate biomarker to select those patients (pts) who will benefit the most. Methods: We evaluated retrospectively pretreatment (baseline) and post-treatment (every 2 months) serum LDH in 94 pts with NSCLC treated with anti-PD1/PDL1. Repeated measures ANOVA, Kaplan-Meier and the proportional COX model were used to examine the association of LDH with overall survival (OS). The cutoff level of LDH was 400 based on the median of the sample. (normal range 105-333 U/L). Results: From July 2013 to February 2016, 94 pts were treated with immunotherapy based on anti-PD1 (77.6%) and anti-PDL1 (22.4%), in trials at VHI. Median age was 62 (39-86). Histological subtypes were: squamous 32.3%, squamous 42.5%, others 4.2%. The OS was significantly different in pts treated with immunotherapy according to baseline LDH, if LDH ≤400 median OS was 8.2 months, while in pts with LDH ≥400 median survival was not reached (Figure 1).

There were statistically significant differences in the evolution of LDH, with better responses if there was a downward trend in LDH levels. In long responding pts (45 of 94 pts), defined as ≥ 3 evaluations (6 months), a LDH level at the time of 6 months treatment below than the baseline LDH predicts better responses (22/45 pts): 68.2% partial response (PR); 19.2% stable disease (SD); 13.6% disease progression (PD). In contrast, when LDH at third evaluation was higher than baseline LDH (23/45 pts): 39.1% PR; 56.5% SD; 4.3% PD, (p=0.022). There were differences between the level of LDH pre and post-progression. 66.67% of patients who progressed had a higher level of LDH at the time of progression than at the previous assessment (p=0.03). Conclusion: LDH may be a potential predictive biomarker of survival benefit conferred by immunotherapy in patients with NSCLC.

Keywords: Immunotherapy, LDH, NSCLC, surrogate biomarker
**POSTER SESSION 3 - P3.02C: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/IMMUNOTHERAPY IT BIOMARKERS – WEDNESDAY, DECEMBER 7, 2016**

**P3.02C-066 HLA-A2 STATUS AND IMMUNE CHECKPOINT INHIBITORS IN ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC) PATIENTS**

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**Background:** The class I human leucocyte antigen (HLA) molecules play a critical role in tumor recognition by T cells and the loss of expression seems to be an escape mechanism of antitumoral immunity. Novel immune-targeting agents or within clinical trials (with pembrolizumab or atezolizumab) were correlated with prognosis (p < 0.001 and p < 0.001). LNR, dNLR (ANC/WBC ANC) and PLR were significantly correlated with survival from immunotherapy beginning (p = 0.01, p = 0.21 and p = 0.03, respectively). An early increase of NLR and dNLR at 2 cycle were prognostic for shorter survival (p = 0.001 and p = 0.001). Increases of ANC and absolute eosinophil count (AEC), and decreases of absolute lymphocytes count (ALC) at 2 cycle were also associated with poor prognosis (p = 0.02, p = 0.02 and p = 0.048 respectively).

**Keywords:** neutrophil-to-lymphocyte ratio, biomarker, NSCLC, immune checkpoint inhibitor

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**P3.02C-068 IMMUNOTHERAPY AGAINST NON SMALL CELL LUNG CANCER (NSCLC): LOOKING FOR PREDICTIVE FACTORS TO AVOID UNINTERRUPTED SHOCKING EFFECTS.**

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**Background:** The immune system recognizes and eliminates certain types of tumor cells, whereas other malignancies are capable of suppressing immune function. For example, a number of cancers cells types express programmed cell death ligand 1 (PD-L1), which binds to its receptor PD-1 on T cells to prevent their activation. High levels of PD-L1 expression are typically associated with poor patient prognosis. Based on these results, recent studies have identified immune-targeting agents (e.g., inhibitors of the PD-1/PD-L1 pathway) to stimulate the immune system, allowing the body's natural defenses to combat the tumor. To determine which patients are suitable candidates for receiving immunotherapy, levels of PD-L1 expression are often determined from tumor biopsies, but tumor heterogeneity can confound these results and obtaining tumor tissue is often not feasible. To enable non-invasive detection and sequential monitoring of tumor-associated PD-L1 expression we have developed a highly sensitive method of detecting PD-L1 levels in circulating tumor cells (CTCs). Here we sought to analytically validate the PD-L1 assay by introducing PD-L1-positive (H358) and PD-L1-negative (BT474) cells into control blood samples, and measuring detection accuracy. Methods: PD-L1 expression levels on carcinoma cell lines were identified by flow cytometry. For analytical validation, H727, BT474 H358, HCC78 and H820 cells were spiked in to CEE-SureTM blood collection tubes, in replicates and on different days, incubated overnight and thereafter processed. The leukocyte fraction was incubated with our pan-CTC antibody capture cocktail, labeled with biotinylated secondary antibody, followed by enrichment in our streptavidin coated microfluidic channels. Enriched cells were stained for DAPI, cytokeratin, CD45, PD-L1 (clone 28-8) and CEE-Enhanced (pan-CTC stain). After automated fluorescence scanning, 400 spiked tumor cells per microfluidic channel were identified and average PD-L1 intensities were quantified for each cell and cut-off criteria were determined. Results: In our microfluidic PD-L1 assay we demonstrate H727 and BT474 cells to be negative for PD-L1, while H358 cells have low-medium and H820 cells high PD-L1 expression. We determined a cut-off value (average fluorescence intensity value) that yielded 100% concordance between the result of the PD-L1 test and the identity of the introduced cell lines, based on a 95% confidence level and a 3.9% negative cut-off. Conclusion: The Biocept PD-L1 assay can accurately detect added CTCs expressing PD-L1 in blood samples. This ability affords a way to identify patients likely to benefit from immune therapy as well as monitor the efficacy of such treatments.

**Keywords:** Immunotherapy liquid biopsy, PD-L1 Circulating Tumor Cells, Circulating tumor cells, PD-L1 Liquid biopsy
Background: The NLR, a marker of systemic inflammation, has been associated with outcomes in multiple cancers. In patients (pts) with metastatic melanoma treated with ipilimumab, pre-therapy NLR < 5 has been associated with improved progression-free survival (PFS) and overall survival (OS). However, the utility of NLR as a marker of outcomes in pts with NSCLC is not well known. Methods: We conducted a retrospective cohort study of pts with advanced NSCLC treated with programmed-death 1 (PD-1) inhibitors. Results: Of 494 pts (432 treated with Nivolumab and 62 with Pembrolizumab), the NLR was 5.5 (IQR, 3.1 – 9.4), with NLR < 5 in 73 pts (42%). Advanced pre-treatment NLR ≥ 5 was associated with improved progression-free survival (PFS) and overall survival (OS) (median 2.8 vs. 1.9 months; adjusted for the aforementioned clinical and demographic factors, pts with baseline NLR ≥ 5 had significantly improved PFS (median 2.8 vs. 1.9 months; adjusted for the aforementioned clinical and demographic factors, pts with baseline NLR ≥ 5 had significantly improved PFS (median 2.8 vs. 1.9 months; adjusted for the aforementioned clinical and demographic factors, pts with baseline NLR ≥ 5 had significantly improved PFS (median 2.8 vs. 1.9 months). Conclusion: Pre-therapy NLR is independently associated with PFS and OS in advanced NSCLC pts treated with nivolumab. It is unclear whether this marker is predictive or prognostic. Prospective studies are warranted to determine the utility of NLR in predicting outcome in the context of other biomarkers, such as PD-1 expression.

Keywords: Nivolumab, non-small cell lung cancer, Neutrophil-to-lymphocyte ratio, Immunotherapy

References:
microenvironment or could deplete effector cells. Moreover, auto-immune responses could cause potential side effects. To overcome these problems, we exploited near infrared photoimmunotherapy (NIR-PIT) at the tumor to deplete only intratumoral-Tregs. Methods: F(ab')2 fragments of an anti-mouse CD25 antibody, PC61.3, were generated and conjugated with a phthalocyanine dye, IRDye-700DX (anti-CD25-F(ab')2, IRDye-700DX, IRDye-700). In vitro NIR-PIT effect was examined against CD25-expressing T-lymphocytes, HT2-cloned A5E-cells. In vivo CD25-target-NIR-PIT was performed after an intravenous injection of the conjugate to mice bearing subcutaneous, luciferase transfected, LL2 (Lewis lung carcinoma, LL2-luc). Tumor-volume, bioluminescence signals (BLI), and Immune responses following the therapy were examined Results: In vitro NIR-PIT-induced cytotoxicity was light-dose-dependent. Local CD25-target-NIR-PIT selectively depleted intratumoral-Tregs; yet, Tregs in any other organs were not affected. The local CD25-target-NIR-PIT induced an intratumoral rapid activation and cytotoxic action of CDT-T cells and NK-cells. This led to significant reductions of tumor-volume (p < 0.0001) and BLI (p < 0.05) and prolonged survival (p < 0.0001) compared to non-treated controls. Intriguingly, this local CD25-target-NIR-PIT induced a transient systemic cytokine storm and anti-tumor-effects on distant non-irradiated specific tumors. Effects of local CD25-target-NIR-PIT were significantly (p < 0.0001) inhibited by a CD8-, NK-, or INFg-depletion, suggesting the anti-tumor roles of CDT T-cells and NK-cells. Conclusion: Depletion of intratumoral-Tregs with a local CD25-target-NIR-PIT rapidly induced CDT T-and NK-cell activation, thereby restoring local anti-tumor immunity. Consequently, activated immunity led to regression of not only NIR-PIT-treated-tumors but also non-NIR-light-exposed-tumors in separate parts of the body (Fig). These observations suggest that local CD25-target-NIR-PIT may be a promising new strategy for cancer immunotherapy.

Keywords: local cancer immunotherapy, Lewis lung cancer, photoimmunotherapy, regulatory T cell

Poster Session 3 - P3.02C: Advanced NSCLC & Chemotherapy/Targeted Therapy/Immunotherapy
IT Biomarkers - Wednesday, December 7, 2016

P3.02C-072 Predictive Immunologic Markers of Response to Nivolumab in Non-Small Cell Lung Cancer

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Background: Nivolumab has become a consolidated therapeutic approach for previously treated non-small cell lung cancer (NSCLC); however, consistent prognostic and predictive factors are still lacking. Since these agents act by enhancing the immune response against tumor cells, it is possible that distinctive patterns in the circulating T cell sub-populations might be associated with different responsiveness. The aim of this study is to determine whether variations in these sub-populations might predict objective response to nivolumab in NSCLC. Methods: Blood samples were collected and stored from patients receiving nivolumab (3 mg/kg every 14 days) for advanced NSCLC with a single-institutional, non randomised, phase II trial, approved by the Ethical committee of the San Martino Hospital – National Institute for Cancer Research, Genova, Italy. The sample collection was performed before each administration for 4 consecutive cycles, followed by computed tomography (CT)-scan. Response assessment was performed with the response evaluation criteria in solid tumors (RECIST) 1.1 and the immune-related response criteria (iRECIST); responses were defined as partial response (PR), stable disease (SD), and progressive disease (PD). Additional CT-scans were performed at 4 cycles intervals. Peripheral blood mononuclear cells (PBMC) were analyzed for the frequency of the major adaptive cell subsets, including B cells, natural killer (NK), and T-cells; the latter were divided into CD8+ T-cells, exhausted CD8+ T-cells, CD4+ T-cells, and regulatory T cells (Tregs); the relative frequencies and the ratios between the sub-populations at each sample collection were compared with radiological response. Results: Fifty-four patients were considered eligible: median age=70 (44-85); male/female: 70%/30%; current or former smokers: 87%; non-squamous/squamous histology: 80%/20%. Patients achieving PR at the first RECIST assessment had a significant upregulation of Tregs (CD4+ Foxp3+ CD39+ cells; p = 0.021), as well as a decreased CDT+/Treg ratio (p = 0.033) at the baseline sample. Conversely, patients experiencing PD at the first RECIST assessment had a significantly upregulated CDT+/Treg ratio at cycle 2 (p = 0.029). Finally, patients experiencing PD at rRC had a higher proportion of activated T cells (CD1+ CD69+ CD3+) compared to the other patients (p = 0.018) at cycle 2. Conclusion: The proportions of Tregs and activated T cells appear to be correlated with different responses to nivolumab according to RECIST and iRECIST. While the immunologic mechanism at the basis of these findings has to be defined, further studies involving PBMC as predictors of response to immunotherapy for NSCLC are highly advised.

Keywords: non-small cell lung cancer, Nivolumab, predictive biomarkers, lymphocytes

Poster Session 3 - P3.02C: Advanced NSCLC & Chemotherapy/Targeted Therapy/Immunotherapy
IT Biomarkers – Wednesday, December 7, 2016

P3.02C-073 Evidence suggesting a dichotomous “Present vs Absent” Determinant of PDL1 Inhibitor Efficiency in Non-Small Cell Lung Cancer (NSCLC)

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Background: NSCLC survival and progression-free survival (PFS) curves often follow first-order kinetics (Stewart, Lung Cancer 2011;71:217). We hypothesized that the number of curve decay phases reflects number of biologically distinct subpopulations with distinct rates of progression or death that are determined by dichotomous (present vs absent) factors. In NSCLC, some PDL1-negative patients respond to PDL1 inhibitors, while some PDL1 strongly-positive patients do not. Methods: We used “arohatgi.info/ WebPlotDigitizer/app/” to digitize published NSCLC PDL1 inhibitor PFS curves and used GraphPad Prism5 for nonlinear regression analyses (one-phase and two-phase; constraints: Y_1=100, plateau=0). Results: 26 of 28 fits 2 phase decay models with R^2>0.90, with distinct “fast progression” (FP) and “slow progression” (SP) subgroups. In studies with PFS curves for different PDL1 expression groups, patients with higher PDL1 tended to have a larger SP subgroup, although some with low PDL1 had slow progression and some with high PDL1 had fast progression (see Table).

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Conclusion: 1) PFS-curve nonlinear regression analysis identified 2 distinct subgroups (FP/SP) with differing degrees of benefit from PDL1 inhibitors. 2) Some PDL1-low patients had SP while some PDL1-high patients had FP, although there was a trend of PDL1-high than PDL1-low. 3) The observation of 2 distinct subpopulations leads us to hypothesize that there is a dichotomous variable (eg, gene mutation, deletion, amplification or silencing) driving PDL1 inhibitor benefit. The trend to higher benefit with high PDL1 expression, but inexact prediction of benefit by PDL1 expression is similar to the published trend seen with response vs PDL1 expression, and suggests that this dichotomous variable is linked to but distinct from direct PDL1 expression. 4) The published observation that high mutation burden is associated with PDL1 inhibitor benefit suggests that high mutation burden increases the probability of presence of a putative dichotomous favorable factor. We observed similar outcomes in other tumor types.

Keywords: predictive factors, PDL1 inhibitors, NSCLC

Poster Session 3 – P3.02C. Advanced NSCLC & Chemotherapy/Targeted Therapy/Immunotherapy
It Biomarkers – Wednesday, December 7, 2016

P3.02C-074 Evaluation of a Pretreatment Serum Tests for Nivolumab Benefit in Patients with Non-Small Cell Lung Cancer
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Background: Anti-PD1 inhibitors are becoming the treatment of choice for 2nd line non-small cell lung cancer (NSCLC). While existing testing for PDL1 expression may correlate with anti-PD1 benefit, current data do not support these tests to be sufficient to guide therapy. We evaluated the utility of a serum-based pre-treatment test first developed to identify patients benefiting from anti-PD1 therapy in metastatic melanoma in patients with NSCLC. These results were compared to the data obtained from the application of the established VeriStrat® test to the same samples. Methods: 60 advanced NSCLC patients treated with nivolumab in an observational study were included. Pretreatment serum samples were classified using the fully locked mass spectrometry-based multivariate tests BDX008 and VeriStrat. BDX008 generates a classification of positive (BDX008+, good outcomes) or negative (BDX008-, poor outcomes); VeriStrat classifies samples as Good and Poor. The molecular status assessed in 32 p (KAS mutation 10p). Immunotherapy was the second-line treatment in 26p with a median number of doses received of 5 (range 2-27). Median OS was 12 months (95% CI 2–21) and median PFS was 6 months (95% CI 0.7-2) from the start of check points inhibitors. Overall survival rate at 12 months was 40%. Immun-related adverse events were observed in 15p (37.5%), including 7 grade 3-4 events (17.5%). No drug-related death occurred. We found that there was a significant association between the risk of toxicity and the increased number of eosinophils between the first reassessment and the baseline measurement OR, 6, 0.014. At the time of the first reevaluation, 28p had progression disease (PD), 6 partial response (PR) and 6 stable disease (SD). In 22/28p with progression at first evaluation, CT was realized ≤4 weeks. Pseudoprogression was confirmed in 6/22p (29%). No differences were found in response by gender, EGCG, histology, KRAS or tobacco, smoking status, anti-PD-1 vs anti-PD-L1, or drug used. 15/18p with clinical benefit (PR+SD+psuedoprogression) had basal level of eosinophils ≥1000 mm3, (p 0.003 OR 0.114) whilst correlation between response and basal lymphocytes was not statistically significant (p 0.35 OR 0.58). One of 18p with clinical benefit had levels of lymphocytes at the first evaluation ≥1000 mm3 versus 10/22p with P(DP 0.013, HR 0.33) whilst levels of eosinophils ≥1000 mm3 at the first evaluation was not statistically significant (p 0.052 HR 0.26). Conclusion: Our very preliminary results suggest that lymphocytes and eosinophils could help us to characterize activity and toxicity of immunotherapy treatments. Further studies are guaranteed.

Keywords: NSCLC, Immunotherapy, Biomarkers

Poster Session 3 – P3.02C. Advanced NSCLC & Chemotherapy/Targeted Therapy/Immunotherapy
It Biomarkers – Wednesday, December 7, 2016

P3.02C-075 Could Blood Levels of Lymphocytes and Eosinophils Help Us to Identify the Efficacy or Toxicity of Immunotherapy?
Eugenio Olmedo1, Jacobo Muñoz Del Toro1, Luis Gómez2,Josefa Perez Templado1, Ana Gomez1, Pablo Reguera1, Marla Góin1, Ainhoa Madrigar1, Olga Martinez1, Javier Molina1, Maria Villamayor2, Victor Albarrán1, Arantza Barquin1, Cristina Saavedra1, Ainara Soría1, Teresa Alonso1, Pablo Gajate1, Enrique Grande1, Pilar Garrido1. 1Medical Oncology Department, University Hospital Ramon Y Cajal, Madrid/Spain; 2Radiology Department, University Hospital Ramon Y Cajal, Madrid/Spain

Background: Immune checkpoint blockade have demonstrated durable responses and improvement in overall survival in approximately 20% of unselected patients with advanced non-small cell lung cancer (NSCLC). To develop reliable, validated biomarkers to identify those subgroups of patients most likely to benefit remains a challenge. Methods: We retrospectively analyzed pretreated advanced NSCLC patients (n) receiving anti-PD1 or anti-PDL1 inhibitors at our institution. The immune-related response Criteria (IRC) was used for response evaluation. Basal and at 6 weeks lymphocytes and eosinophils counts were correlated with efficacy and toxicity. Results: 44p were treated between April and December 2015. We realized evaluation of response in 40 p. 13p received Atezolizumab, 23 p Nivolumab and 4 p Pembrolizumab. Patients characteristics: 68% males, median age 63 years, 62% non-squamous histology, 3% never-smoker, PS 0/1/2 in 43/50/7%. The molecular status assessed in 32 p (KAS mutation 10p). Immunotherapy was the second-line treatment in 26p with a median number of doses received of 5 (range 2-27). Median OS was 12 months (95% CI 2–21) and median PFS was 6 months (95% CI 0.7-2) from the start of check points inhibitors. Overall survival rate at 12 months was 40%. Immun-related adverse events were observed in 15p (37.5%), including 7 grade 3-4 events (17.5%). No drug-related death occurred. We found that there was a significant association between the risk of toxicity and the increased number of eosinophils between the first reassessment and the baseline measurement OR, 6, 0.014. At the time of the first reevaluation, 28p had progression disease (PD), 6 partial response (PR) and 6 stable disease (SD). In 22/28p with progression at first evaluation, CT was realized ≤4 weeks. Pseudoprogression was confirmed in 6/22p (29%). No differences were found in response by gender, EGCG, histology, KRAS or tobacco, smoking status, anti-PD-1 vs anti-PD-L1, or drug used. 15/18p with clinical benefit (PR+SD+psuedoprogression) had basal level of eosinophils ≥1000 mm3, (p 0.003 OR 0.114) whilst correlation between response and basal lymphocytes was not statistically significant (p 0.35 OR 0.58). One of 18p with clinical benefit had levels of lymphocytes at the first evaluation ≥1000 mm3 versus 10/22p with P(DP 0.013, HR 0.33) whilst levels of eosinophils ≥1000 mm3 at the first evaluation was not statistically significant (p 0.052 HR 0.26). Conclusion: Our very preliminary results suggest that lymphocytes and eosinophils could help us to characterize activity and toxicity of immunotherapy treatments. Further studies are guaranteed.

Keywords: NSCLC, Immunotherapy, Biomarkers

Poster Session 3 – P3.02C. Advanced NSCLC & Chemotherapy/Targeted Therapy/Immunotherapy
It Biomarkers – Wednesday, December 7, 2016

P3.02C-076 Correlation of Neutrophils to Lymphocyte Ratio (NLR) with Clinical Benefit from Checkpoint Inhibitors in Advanced Lung Cancer
Alona Zer, Mike Sung, Kanwalpreet Wala, Leila Khaja, Manjula Maganti, Catherine Labbe, Frances Shepherd, Penelope Bradbury, Ronald Feld, Geoffrey Liu, Melissa Iazzi, Dianne Zawisza, Nazanin Nouriany, Natasha Leighl. Princess Margaret Cancer Centre, Toronto/ON/Canada

Background: Immune checkpoint inhibitors (ICI) have become standard therapy after platinum failure in advanced non-small cell lung cancer. ICI response patterns differ from chemotherapy with the potential for delayed regression and pseudo-progression in patients benefiting from treatment. Additional markers beyond PDL1 expression are needed to assist in patient selection, response evaluation and treatment decision-making. Methods: The relationship between clinical outcome (response, treatment duration, survival) and hematologic parameters (absolute neutrophil count [ANC], neutrophil to lymphocyte ratio [NLR]) was explored in a cohort of patients treated with ICIs at a major cancer centre from 05/2013 to 05/2016. Clinical benefit was defined as achievement of complete or partial response (CR, PR) or stable disease (SD) at 8 weeks. Hematologic parameters at baseline (T0) and on treatment (T1=2 or 3 weeks, T2=8 weeks) were included. Results: Of 101 patients treated with ICIs at a major cancer centre from 05/2013 to 05/2016. Clinical benefit was defined as achievement of complete or partial response (CR, PR) or stable disease (SD) at 8 weeks. Hematologic parameters at baseline (T0) and on treatment (T1=2 or 3 weeks, T2=8 weeks) were included. Results: Of 101
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POSTER SESSION 3 - P3.02C: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/IMMUNOTHERAPY
IT BIOMARKERS – WEDNESDAY, DECEMBER 7, 2016

P3.02C-077 CARDIAC TROPONIN-I ELEVATION IN PATIENTS WITH NON- SMALL CELL LUNG CANCER DURING PD1/PDL1 INHIBITION WITH NIVOLUMAB
Erika Rijavec1, Carlo Genova1, Matteo Sarocchi1, Simone Musi1, Eleonora Argoscillo1, Andrea Bellodi1, Giulia Barletta1, Federica Biello1, Giovanni Rossi1, Claudia Maggioni1, Maria Giovanna Dal Bello1, Claudio Brunelli2, Francesco Grossi1
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Background: Immune check-point inhibitors are effective for the treatment of advanced non-small cell lung cancer (NSCLC); however, their mechanism of action is associated with peculiar immune-related adverse events (irAEs). While cardiac irAEs are seldom reported, animal data suggest that the myocardium might be sensitive to PD1/PDL1 impairment. Minimal alterations of Cardiac Troponin-I (CTnI) can identify subclinical cardiac toxicity induced by antineoplastic agents like anthracyclines. The aim of this study is to further investigate irAEs associated with nivolumab treatment. Patients and methods: Serum samples were collected and stored from 61 patients receiving nivolumab (3 mg/Kg every 14 days) for advanced NSCLC within a single-institutional translational research study conducted in the San Martino Hospital – National Institute for Cancer Research, Genova, Italy (approved by the local ethical committee); samples were collected at baseline and at each cycle up to 5 cycles, and then every 2 cycles. Cardiac Troponin-I was retrospectively quantified with the luminescent oxygen channeling immunoassay (LOCI™) optimized on the Dimension Vista® analytical platform (Siemens Healthcare, Lake Success/NY/United States of America). Conclusion: Troponin-I was altered in a considerable number of patients receiving nivolumab, in some cases with no evident concurrent cardiovascular disease or manifest indirect noxae. Although a rationale for immunotherapy-related myocardial inflammation is acknowledged, further investigations on the cardiovascular effects of PD1/PDL1 inhibitors are required to draw meaningful conclusions, such as studies involving prospective cardiovascular assessments of patients receiving these agents.

Keywords: non-small cell lung cancer, Nivolumab, Troponin, cardiotoxicity

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IT Biomarkers – Wednesday, December 7, 2016

P3.02C-079 Immunotherapy in Non Small Cell Lung Cancer (NSCLC): Biomarkers Associated with Early Death


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Background: Immune checkpoint blockade monoclonal antibodies have demonstrated an improvement in the overall survival (OS) of patients with NSCLC. The aim of our research was to explore biomarkers of early death among the routinely used biological parameters in the population diagnosed with advanced lung cancer treated with immunotherapy. Methods: In this retrospective study, we collected blood levels of lymphocytes, eosinophils and lactate dehydrogenase (LDH) before immunotherapy infusion. Inclusion criteria were a diagnosis of stage IV NSCLC, at least one previous line of chemotherapy. Results: 44 patients (p) were treated between April 2014 and December 2015. Thirteen p received atezolizumab, 27 p nivolumab and 4 p pembrolizumab. 70.5% males with a median age of 63 (range 42-82), 29.5% squamous and 2.3% never-smoker patients. Eighteen p had PS 0 (41%), 22p PS1 (50%) and 4p PS 2 (9%). Thirty-one p had ≥(62%) had baseline eosinophils <100 mm3, the risk of early death was higher in 14/18p (78%) had basal LDH levels above the normal range in 8/14 p (55%), was not statistically significant. The risk of early death in the setting of immunotherapy (Weide et al Clin Can Res 2016, and Ferrucci et al BJC 2015). We attempted the same in our lung cancer population. Analyzing some baseline clinical laboratory parameters had predictive value in the setting of immunotherapy (Weide et al Clin Can Res 2016, and Ferrucci et al BJC 2015). We attempted the same in our lung cancer population. We have previously reported that the ratio of absolute neutrophil count (ANC) to absolute lymphocyte count (ALC) has potential as PDL-1 testing, while helpful, is imperfect. Identifying additional indicators is warranted. Studies in melanoma patients demonstrated that indicators is warranted. Studies in melanoma patients demonstrated that baseline serum determination of LDH and eosinophils might help us to identify patients with NSCLC who achieve more benefit from immunotherapy. Futher studies are guaranteed.

Keywords: Immunotherapy, NSCLC, Early death, Biomarkers

Poster Session 3 – P3.02C. Advanced NSCLC & Chemotherapy/Targeted Therapy/Immunotherapy

IT Biomarkers – Wednesday, December 7, 2016

P3.02C-081 Complete Blood Count Parameters as Predictive Factors in Patients with Advanced Non-Small Cell Lung Cancer Treated with Nivolumab

Diana Saravia, Bahar Laderian, Wungki Park, Amrita Desai, Fernando Vargas, Roy Elias, Sean Warsch, Raja Mudad, Chukwuemeka Ikepeazu, Adrian Ishkhanian, Lisa Balfie, Mohammad Jahanzeb

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Background: Checkpoint inhibitors such as nivolumab (anti-PD1) represent a recent breakthrough in the management of patients with advanced non-small cell lung cancer (NSCLC) after disease progression following initial platinum-based therapy. Prospective identification of likely responders remains a challenge as PDL-1 testing, while helpful, is imperfect. Identifying additional indicators is warranted. Studies in melanoma patients demonstrated that analyzing some baseline clinical laboratory parameters had predictive value in the setting of immunotherapy (Weide et al Clin Can Res 2016, and Ferrucci et al BJC 2015). We attempted the same in our lung cancer population. Methods: We performed a retrospective analysis in a patient population with biopsy proven advanced NSCLC who received nivolumab. Patient charts were reviewed to obtain data on demographics, ECOG performance status, stage, number of previous therapies, and baseline complete blood count (CBC), from which the ratio of absolute neutrophil count (ANC) to absolute lymphocyte count (ALC) was calculated. Imaging data for response assessment were available. Univariate analysis was performed to study the association between clinical and demographic parameters and progression-free survival (PFS) using SAS software. Results: In our cohort of 114 patients treated during 2015-2016, the median follow-up was 5.4 months (range 0.15-8), median age was 67 years (range 40-91), and median number of prior therapies was 2. There were 52% males, 60% Caucasians, 32% Hispanics, 8% African Americans, and 75% had ECOG performance status of 0. Our univariate analysis showed the following:

Conclusion: Our data indicates that low baseline ANC/ALC (<5), female gender, and ECOG 0-1 are independent factors associated with significantly favorable
PFS in patients with advanced NSCLC treated with nivolumab. A more detailed analysis of a larger cohort, including data on mutational burden, will be presented.

POSTER SESSION 3 – P3.02C: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/ IMMUNOTHERAPY
IT BIOMARKERS – WEDNESDAY, DECEMBER 7, 2016
P3.02C-082 ALTERED EXPRESSION OF PROGRAMMED DEATH-LIGAND 1 AFTER NEO-ADJUVANT CHEMOTHERAPY IN PATIENTS WITH LUNG SQUAMOUS CELL CARCINOMA
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Background: Programmed-death-ligand 1 (PD-L1) is known to be over-expressed in non-small cell lung cancer (NSCLC). However, the impact of chemotherapy on the altered status of PD-L1 expression has not been examined for NSCLC. The present study was intended to examine the impact of neoadjuvant chemotherapy on PD-L1 expression and its prognostic significance in lung squamous cell carcinoma (SCC). Methods: Matched tumor samples were obtained from SCC patients prior to and after neoadjuvant chemotherapy. The expression of PD-L1 was evaluated by immunohistochemistry. Survival analysis was performed by the Kaplan-Meier method. Results: A total of 76 eligible SCC patients were recruited. There were 51 males and 25 females with a median age of 60 (39-72) years. The smoking status was former (n=46) and never (n=34). Prior to neoadjuvant chemotherapy, PD-L1 expression was identified in 52.6% (40/76) of SCC patients while 61.8% (47/76) were positive for PD-L1 expression after neoadjuvant chemotherapy. Nine patients switched from negative to positive while another two patients’ samples showed the reverse of the above result. Multivariate analysis demonstrated that postoperative expression of PD-L1 was an independent prognostic factor for overall survival (HR=0.5, P=0.003), but not for PD-L1 expression prior to neoadjuvant chemotherapy. Conclusion: Neoadjuvant chemotherapy may up-regulate the expression of PD-L1. As compared with the status of PD-L1 expression prior to chemotherapy, the postoperative expression of PD-L1 is a better prognostic factor for overall survival in SCC.
Keywords: chemotherapy, Squamous cell carcinoma, Programmed death-ligand 1, Overexpression

POSTER SESSION 3 – P3.02C: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/ IMMUNOTHERAPY
IT BIOMARKERS – WEDNESDAY, DECEMBER 7, 2016
P3.02C-083 TREATMENT RELATED ADVERSE EVENTS PREDICT IMPROVED CLINICAL OUTCOME IN NSCLC PATIENTS ON KEYNOTE-001 AT A SINGLE CENTER
Aaron Lisberg, D. Andrew Tucker, Jonathan W. Goldman, Brian Wolf, James Carroll, Jennifer Gao, Henry Hardy, Karolyn Morris, Paulina Linares, Carlos Adame, Marshall Spiegel, Courtney Wells, Jordan Mckenzie, Blanca Ledezma, Melody Mendenhall, Phillip Abarca, Krikor Bornazyan, Jamie Hunt, Sina Famenini, Carroll, Ariana Hardy, Karolyn Morris, Paulina Linares, Carlos Adame, ligand 1, Overexpression
Keywords: chemotherapy, Squamous cell carcinoma, Programmed death-ligand 1, Overexpression

P3.02C-084 PREDICTIVE AND PROGNOSTIC CLINICAL AND PATHOLOGICAL FACTORS OF NIVOLUMAB EFFICACY IN NON-SMALL-CELL LUNG CANCER (NSCLC) PATIENTS
Paloma Martin1, María De Julián2, Javier Perez Alzatozo3, Carmen Salvador Coloma4, José García Sánchez5, Amelia Insa Molla6, María Martín7, Xabier Mielgo Rubio7, Sara Marín8, Ana Blasco Cordellat, Sara Blasco Cordellat9, Regina Gironés10, Paloma Gómez10, Maica Bas Cerda10, Óscar Juan11, Javier Garde-Noguera12
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Background: Imunotherapy with anti-PD1 and anti-PDL1 monoclonal antibodies significantly increases overall response rate (ORR) and overall survival (OS) of patients with advanced NSCLC in comparison with second line conventional chemotherapy. Prognostic and predictive factors able to distinguish those patients with a higher benefit from this immunotherapy are still warranted. Our work retrospectively analyses several clinical, pathological and analytical variables with an eventual potential prognostic and predictive value in daily patients with advanced NSCLC receiving Nivolumab. Methods: A retrospective review of clinical charts of patients with advanced NSCLC from fourteen centres of the GIDO group receiving Nivolumab between May-2015 and May-2016 was performed. Age, sex, stage, Performance Status (PS), location of metastases, presence of tumour-related symptoms and comorbidities, number of organs with metastasis, previous chemotherapy, antiangiogenic and radiotherapy treatments, and analytical data from standard blood count and biochemistry were collected and statistically analyzed. Results: A total of 175 patients fulfilled inclusion criteria. Median age was 61.5 years. One hundred and twenty-eight male (73.1%), 136 ECOG-PS 0-1 (77.7%), 150 stage IV (86.7%) and 135 had non-squamous carcinoma (77.7%). More than one metastatic location vs one location (HR 1.79) were independently associated with longer probability of response to Nivolumab. PS 2 vs 0-1 (HR 1.83), time since the beginning of previous line of treatment <6 vs >6 months (HR 1,70) and more than one metastatic location (22.3%) and 126 had more than one metastatic location (72%). 140 patients were evaluable for response, the ORR was 15.7%, median Progression Free Survival was 2.8 months, and median OS 8.51 months. Stage III (OR 3.57) and stage IV (OR 6.3) were more associated with worse overall OS in multivariable analysis. Conclusion: Poor Performance Status, short period of time since the beginning of previous treatment and more than one metastatic location are the clinical pathological
features associated with poorer prognosis in patients with advanced NSCLC treated with Nivolumab. Limitations of the study are the small numbers and the retrospective nature.

Keywords: Prognostic factors, lung cancer, Nivolumab

P3.02C-085 NEUTROPHIL/LYMPHOCYTE RATIO IN ADVANCED NON-SMALL CELL LUNG CANCER: CORRELATION WITH PROGNOSIS AND RESPONSE TO ANTI-PD1 THERAPY

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Background: The Neutrophil/Lymphocyte ratio (NLR), calculated from peripheral blood tests, represents an independent and easily available prognostic biomarker in numerous cancers, including lung cancer. This study aimed to investigate the prognostic role and the correlation with the therapeutic response of baseline NLR in patients with advanced Non-small cell lung cancer (a-NSCLC) submitted to anti-PD1 therapy. Methods: Nivolumab (3 mg/kg intravenously by rapid injection every 14 days) was administered to 47 patients (6 women, 41 men) with a-NSCLC. The mean age of patients was 67 years (range 40-83, SD 9.07), while the histotype was: 28 adenocarcinoma, 18 squamous, 1 adenosquamous. 68% of patients were current/former smokers. 25/47 patients (53%) received more than 2 previous lines of therapy. The baseline absolute neutrophil and lymphocytes count and the Neutrophil/Lymphocytes ratio were recorded. Time to progression (TTP) was statistically evaluated by Kaplan-Meier method; univariate analysis was conducted by Cox regression method. Results: A median of 7.8 (range 1-20) cycles of therapy was administered. A better TTP (3 months vs 1.5 months; Cox regression rate (Hazard Ratio) 1.00018, p= 0.003 (CI 1.000041-1.000195) was observed in patients with a lower absolute baseline Neutrophil count (Less than 7500); conversely, a higher absolute Lymphocyte baseline count (HR 0.9994947, p= 0.055 (CI 0.9989785-1.000011)). NLR was correlated with Time to Progression (TTP), that was longer in patients with NLR less than 4 (3.71 months vs 1.87; Cox regression rate (HR) 1.144335, p= 0.001 (CI 1.068327-1.22575) (Figure)

Conclusion: These preliminary findings highlight the correlation between the NLR and clinical outcome of a-NSCLC patients treated with anti-PD1. Further investigation in this setting is warranted, both to confirm the prognostic role and to investigate if NLR and the microenvironmental inflammatory alterations could predict the response to immune-checkpoint inhibitors.

Keywords: advanced NSCLC, Neutrophils/Lymphocytes ratio, Anti-PD1 therapy

P3.02C-087 THE RELATIONSHIP OF TILS AND PD-L1 EXPRESSION IN NSCLC ADENOCARCINOMA IN LITTLE TO NON-SMOKERS WITH DRIVER MUTATIONS AND OUTCOME PARAMETERS

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Background: Culminating evidence shows the importance of the immune response in NSCLC and other cancer types. TILs seem to be a marker of good prognosis in many different tumor types, including NSCLC. The prognostic importance of PD-L1 expression in NSCLC remains less clear. This study will contribute more information to this topic in NSCLC and will verify the influence of driver mutations on TILs levels and PD-L1 expression. In addition, the predictive role of TILs and PD-L1 expression in EGFR mutants, who received erlotinib, will be evaluated. Methods: Clinical data, genetic analysis and tumor biopsies of the FIELT cohort (stage IIIa or IV NSCLC patients with little or non-smoking history) were retrospectively evaluated. PD-L1 expression was evaluated with a PD-L1/PD-L1 IHC double staining. TILs were evaluated on H&E slides, using the method developed by an international working group under direction of R. Salgado. Results: Measuring tumoral TILs on H&E slides proved to be reproducible (ICC=0.74). The measurement
of intratumor TILs (ICC=0.16) did not reach the cut-off ICC of 0.70. There was no difference in stromal TILs counts in KRAS (p=0.454) and EGFR (p=0.962) mutant tumors compared to their respective wild type tumors, nor was there any difference in STILs counts between KRAS and EGFR mutants (p=0.605). The median OS in the general population was 49 weeks. There was a significant difference in median OS between the stromal TILs high tumors and the stromal TILs low tumors (68 weeks vs. 35 weeks respectively; p=0.003). A similar observation was made in the KRAS mutant tumors (95 weeks vs. 12 weeks; p=0.003). In the EGFR mutants no significant difference in median OS could be found according to the stromal TILs counts (p=0.65). There was no difference in the stromal TILs counts of EGFR mutants who responded (p=0.160) or showed clinical benefit (p=0.621) after receiving erlotinib, compared to those who did not. The analysis of the PD-1/PD-L1 double staining has been postponed. Results will be available by the end of August 2016. Conclusion: The results of the current study reinforce the prognostic role of TILs in NSCLC. Furthermore, this is the first study to confirm that the used scoring method on H&E slides is reproducible in NSCLC. This study is also the first to report about the relation between driver mutation and TILs, with results suggesting that the immune system plays a more crucial role in KRAS mutants than in EGFR mutants.

Keywords: Tumour infiltrating lymphocytes, PD-1/PD-L1 expression, Advanced Non-Small Cell Lung Carcinoma

Conclusion: Lymph nodes may be a particularly susceptible area to AR to PD-1 axis inhibitors. Defects in B2M leading to loss of tumor MHC-1 presentation may represent a unique mechanism of AR to immune checkpoint inhibitors. Further studies to determine the frequency of defects in antigen presentation machinery in tumors with resistance to PD1 axis inhibitors are warranted.

Keywords: Acquired resistance, beta-2 microglobulin, PD-1, PD-L1

P3.02C-088 ACQUIRED RESISTANCE TO PROGRAMMED DEATH-1 AXIS INHIBITORS IN NON-SMALL CELL LUNG CANCER (NSCLC) Jungmin Choi1, Ryan Sowell1, Anna Truini1, Kurt Schalper2, Anna Wurtz3, Guoping Cai4, Katherine Hastings4, Mary Ann Meink4, Edward Kaufman5, Paula Kavathas5, Susan Koech6, David Rimm3, Sarah Goldberg5, Anne Chiang4, Richard Lifton1, Roy Herbst4, Katerina Politi2, Scott Gettinger7

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Background: Programmed death-1 (PD-1)-axis inhibitors are increasingly being used to treat patients with advanced NSCLC. Despite durable responses relative to chemotherapy, resistance to such therapy develops in the majority of responders, with median duration of response from 12-17 months. Mechanisms of acquired resistance (AR) to PD-1 axis inhibitors are poorly understood. Methods: Patients with advanced NSCLC and acquired resistance (AR) to PD-1 axis inhibitor therapy were enrolled in an IRB approved repeat biopsy protocol allowing collection of clinical data, archived and fresh tumor tissue, and blood for analysis. Molecular analyses including whole exome sequencing of pre-and post-treatment tumor specimens were performed. Results: Twelve cases were available for analysis (table 1). Eight and two patients developed resistance limited to lymph nodes (LN) and adrenal gland respectively. The two remaining patients experienced tumor progression in LNs with other sites of tumor growth (one in liver, one in lung). Nine patients had sufficient archived pre-PD-1 axis inhibitor tumor tissue for analysis/ comparison, leaving three unpaired cases. Genomic analysis of tumor specimens identified two patients with acquired tumor beta-2-microglobulin (B2M) defects at resistance. A patient derived xenograft generated from one of the resistance samples (patient #6) lacked production of B2M protein and did not express surface MHC-1. Additional analyses including immunophenotyping with multiplexed quantitative immunofluorescence on these and other patient samples are ongoing.

Conclusion: The results of the current study reinforce the prognostic role of TILs in NSCLC. Furthermore, this is the first study to confirm that the used scoring method on H&E slides is reproducible in NSCLC. This study is also the first to report about the relation between driver mutation and TILs, with results suggesting that the immune system plays a more crucial role in KRAS mutants than in EGFR mutants.

Keywords: Tumour infiltrating lymphocytes, PD-1/PD-L1 expression, Advanced Non-Small Cell Lung Carcinoma

P3.02C-089 IMMUNOCHEMIC: A PROSPECTIVE NIVOLUMAB MONOTHERAPY COHORT IN ADVANCED NON-SMALL CELL LUNG CANCER PATIENTS IN ROUTINE CLINICAL PRACTICE Shobanya Elvarathnam1, Christos Chouaid2, Nadine Thiriat2, Laurence Jabot2, Gaelle Rousseau-Bussac2, Caroline Jaskowiec2, Florent Vinas2, Stephanie Poullain1, Isabelle Monnet1

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Background: In France, in May 2015, Nivolumab early access program was established for patients with advanced NSCLC progressing during or after platinum-based chemotherapy. There is little evidence of Nivolumab use out of clinical trials. We report here one year of Nivolumab use in a French University hospital. Methods: Observational prospective review of patients with advanced NSCLC treated with Nivolumab monotherapy (3 mg/kg/2weeks) in our center, in routine clinical practice. Patients in clinical trial were excluded. Analyze was done on clinico-pathological features, tolerance and outcomes. Results: 63 patients were included (men: 76.1%, age: 65 (range: 40–78), squamous: 33.3%, smoker: 93.7%, PD-L1 negatives: 98.4%, unknown PD-L1: 70%, at least one significant comorbidity: 54%; performs status 0/1/2: 34%/49%/17%; cerebral metastasis: 38%; nivolumab as second, third and more than third lines: 38%/38%/24%. Median number of nivolumab cycles: 6 (1-24), more than 12 cycles: 20.6% Disease control rate : 59% (3 complete responses); Clinically significant adverse event: 13 (20%) patients (asthenia: 4 patients, grade 2 to 4 colitis: 3 patients, pneumoniae: 3 patients, nephritis: 1 patient). After Nivolumab, 50% of the patients received another systemic therapy. Two patients were able to go back to work. Conclusion: In real life setting, nivolumab had the efficacy level reported by pivotal clinical trial but with a higher rate of clinically significant adverse events, particularly colitis.

Keywords: outcomes, real world setting, Immunotherapy, non small cell lung cancer
P3.02C-090 THE ROLE OF ERCC-1 POLYMORPHISMS AS PREDICTIVE BIOMARKER OF RESPONSE TO RIVOLVAC IN ADVANCED NSCLC
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Background: Programmed death1 (PD-1) pathway is a negative feedback system limiting T cell activity in normal tissues, frequently upregulated by tumors to escape immune destruction. Blockade of this pathway with anti PD-1 antibodies has shown significant clinical activity in different cancer types; nevertheless it is still unclear why some patients respond to immunotherapies while others do not. Recently it was observed that cancers with higher somatic mutation burden, as tumors with genome instability due to DNA repair defects, develop more elevated anti PD-1 induced neoantigen specific T cell response which results into increased susceptibility to PD-1 blockade. We hypothesize that NSCLCs with polymorphisms of ERCC-1 gene (encoding for a key enzyme of DNA nucleotide excision repair pathway) may be more responsive to PD-1 blockade than ERCC-1 proficient NSCLCs as result of higher rates of mutation due to their genetic instability. Methods: We evaluated the rs11615, rs3212986 and rs2298881 ERCC-1 polymorphisms by pyrosequencing analysis on tumor DNA of stage IV previously treated NSCLC patients receiving nivolumab 3 mg/kg q2w. Between July 8, 2015 and Jan 19, 2016, we enrolled 24 NSCLC patients to receive nivolumab. Patient characteristics were as follows: M/F =18/6, median age (range) = 65 (49-80); ECOG PS, 0/1/2/22; sqNSCLC/non sq NSCLC = 6/18; smokers/non-smokers/former smokers = 10/2/12; EGFR status, mutant/wildtype/unknown unknown = 7/17/1; median nivolumab cycles delivered (range) = 9 (1-32). No patients presented rs11615 and rs2298881 polymorphisms. 8 patients were positive for the rs3292886 polymorphism. The rate of objective response for the entire population was 25% (95% CI, 10 to 47). The ORR was significantly higher in NSCLC patients positive for rs3212986 polymorphism than wild-type (62.5% (95% CI, 25 to 92) vs. 6% (95% CI, 0 to 30), P=0.006). Among patients positive for rs3212986 polymorphism, median PFS was not reached. In contrast wild-type patients presented a median PFS of 2.0 months (0.2; 95% CI, 0.07 to 0.58, P<0.004). Conclusion: This study suggested that rs3212986 polymorphism is associated with a higher RR and PFS in advanced NSCLC patients treated with nivolumab. Confirmation of these results in a validation set is ongoing.

Keywords: PD-1, ERCC-1, Nivolumab, Polymorphisms

P3.02C-091 FINAL PHASE IB RESULTS OF RNACTIVE® CANCER VACCINE BI 1361849 AND LOCAL RADIATION AS MAINTENANCE THERAPY FOR STAGE IV NSCLC
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Background: Preclinical studies demonstrated that local radiotherapy (RT) acts synergistically with RNAactive vaccines to increase tumor-infiltrating immune cells and enhance anti-tumor effects. BI 1361849 (CV9202) is an immunotherapeutic cancer vaccine comprising optimized mRNA constituents (RNActive) encoding six NSCLC-associated antigens. Here we report clinical outcomes and immune response data of a phase Ib study, employing local BI 1361849 in advanced NSCLC. Methods: Patients with stage IV NSCLC and a response or stable disease after first-line chemotherapy or therapy with an epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) were enrolled in three cohorts based on histological and molecular NSCLC subtypes (non-squamous vs. squamous vs. EGFR-mutated NSCLC). Patients received two initial vaccines with BI 1361849 prior to local RT to the primary tumor or a metastatic lesion (four consecutive daily fractions of 5 Gy), followed by further vaccinations until start of another treatment. Maintenance Pemetrexed (mp) and EGFR-TKIs were continued according to the label. Primary endpoint was safety; secondary endpoints included objective response, PFS and OS. Cell-mediated immune responses were measured ex vivo by multifunctional intracellular cytokine staining, IFNγ ELISpot, and ELISA in pre- and post-treatment blood samples. Results: 26 pts were enrolled. 15 pts received mp, 2 two received EGFR Tki. Most frequent AE were mild to moderate injection-site reactions and flu-like symptoms. Two pts experienced BI 1361849-related grade 3 AEs (fatigue, pyrexia). No BI 1361849-related SAE or grade 4 AE was reported. Interim results indicate one confirmed PR in a patient receiving mp and SD in 13/25 evaluable pts (52%, 8 pts on mp, 3 pts without maintenance therapy, 2 pts on EGFR-TKI), with two pts showing remarkably long-lasting disease stabilization of up to 72 and 54 weeks, respectively. Shrinkage of lesions outside the irradiated field of ≥15% occurred in 7 pts, all but one receiving mp. Longitudinal assessment of tumor response allows for further insight into patterns of progression. BI 1361849 was capable of eliciting antigen-specific immune responses in the majority of the patients including both non-squamous and squamous lesions. Conclusion: BI 1361849 elicits antigen-specific immune responses and can be safely combined with local RT and mp treatment. Shrinkage of non-irradiated lesions and prolonged disease stabilization was observed in a subset of pts, mainly in combination with mp. Final clinical outcomes and analyses of cellular and humoral immune responses will be presented.

Keywords: Stage IV NSCLC, cancer vaccine, maintenance, local radiotherapy

P3.02C-092 NIVOLUMAB IN MULTI-TRACTED PATIENTS WITH ADVANCED SQ-NSCLC: DATA FROM THE ITALIAN COHORT OF EXPANDED ACCESS PROGRAMME (EAP)
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Background: The prognosis of patients with advanced sq-NSCLC worsens with the increase of the number of treatment lines and no effective therapeutic options were available for those refractory patients so far. Nivolumab demonstrated significant benefits against the SoC docetaxel in 2nd line treatment of advanced sq-NSCLC. In the real life experience of the EAP we could assess the clinical activity and tolerability of nivolumab not only in patients treated in 2nd line but also in patients who had received at least 2 lines of therapy prior than nivolumab. Methods: Nivolumab was provided upon physician request for patients aged ≥18 years who had relapsed after a minimum of 1 prior systemic treatment for stage IIIb/stage IV Sq-NSCLC. Nivolumab 3 mg/kg was administered intravenously every 2 weeks for ≤24 months. Pts included in the analysis had received ≥1 dose of nivolumab and were monitored for adverse events (AEs) using Common Terminology Criteria for Adverse Events (version 4.03). Results: 210 patients, corresponding to 56.4% of the entire Italian cohort (n=372), received nivolumab after at least 2 prior lines of chemotherapy in the EAP: 120 (57.1%), 69 (32.9%) and 21 (10%)
NSCLC EXPANDED ACCESS PROGRAM: EFFICACY AND SAFETY IN PATIENTS WITH BRAIN METASTASES

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Background: The prognosis of NSCLC patients (pts) with brain metastases is still quite poor. These pts usually do not meet the inclusion criteria to be enrolled in clinical trials. Nivolumab Italian Expanded Access Program (EAP) allowed this subpopulation of pts to be included, providing the opportunity to evaluate safety and efficacy of nivolumab treatment in pts with brain metastases. Methods: upon physician written request, nivolumab was provided to pts who met the following inclusion criteria: aged ≥18 years, who had received a diagnosis of squamous NSCLC, and who had relapsed after a minimum of one prior systemic treatment stage for stage IIIb/Stage IV squamous NSCLC. Nivolumab is administrated at the dose of 3 mg/kg every 2 weeks for a maximum duration of 24 months. We describe efficacy and safety of nivolumab in pts who received at least one dose. Adverse events were monitored using Common Terminology Criteria for Adverse Events. Results: from our cohort of 372 patients diagnosed with squamous NSCLC, we report the results of 38 pts with treated and asymptomatic brain metastases. In these pts, with median follow-up of 4.5 months and median number of doses of 6 (range, 1–18), disease control rate was 47.3%, including complete response, 6 partial responses and 11 stable diseases. Treatment beyond RECIST defined progression was allowed, under protocol defined circunstances, in 4 pts. Median progression-free survival was 5.5 months and overall survival was 6.5 months (data lock of April 2016). Among the 38 pts included, only 1 discontinued treatment due to AE (2.6%), whereas 21 pts (55.3%) discontinued treatment for non-toxicity related reasons. Conclusion: although preliminary, these results demonstrate efficacy of nivolumab in squamous NSCLC pts with brain metastases. Safety of nivolumab in these pts is consistent with previously reported data from clinical trials. These results suggest nivolumab could be beneficial in this subpopulation of pts with unfavourable prognosis.

POSTER SESSION 3 – P3.02C: ADVANCED NSCLC & CHEMOTHERAPY/TARGETED THERAPY/IMMUNOTHERAPY IT CLINICAL – WEDNESDAY, DECEMBER 7, 2016

P3.02C-095 ITALIAN NIVOLUMAB EXPANDED ACCESS PROGRAMME: EFFICACY AND SAFETY DATA IN SQUAMOUS NON SMALL CELL LUNG CANCER PATIENTS

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Background: the non-squamous NSCLC patients who have brain metastases have a poor prognosis due to the limited effective treatment options, with median survival of 5 months. Nivolumab is a monoclonal anti-PD-1 antibody, which has shown activity in this patient group both in phase I/II trials and real-life settings. This study aimed to evaluate the efficacy and safety of nivolumab treatment in pts with brain metastases. Methods: an Italian EAP was proposed since January 2015. Patients with non-squamous NSCLC with brain metastases were eligible for enrolment. The study consisted of two stages: in the first stage, up to 40 pts were enrolled, and in the second stage, the recruitment was opened to 20 more pts. Data were collected retrospectively. Results: at the time of data cut-off, November 2016, 60 pts were included in the study. Among all included pts, 41 (68.3%) had lung adenocarcinomas, 4 (6.7%) had lung squamous carcinomas, 7 (11.7%) had non-small cell lung cancer not further specified and 2 (3.3%) had large cell neuroendocrine carcinoma. Median overall survival was 5 months (range 0.5–26 months). The most common adverse events were rash (18.3%), pruritus (11.7%), arthralgia (10.0%), nausea (7.0%) and nasopharyngitis (7.0%). Conclusion: this is the fist Italian retrospective study on the safety and efficacy of nivolumab treatment in pts with brain metastases. Our results confirm the efficacy and safety of nivolumab in Italian NSCLC pts with brain metastases.
Background: Nivolumab monotherapy has shown survival benefit in patients (pts) with melanoma, lung cancer, renal cell carcinoma and head and neck cancer. The experience of pts and physicians in routine clinical practice is often different from those in a controlled clinical trial setting. Here, we report efficacy and safety of nivolumab monotherapy in pts with squamous non small cell lung cancer (Sq-NCSLC) treated in the nivolumab Expanded Access Programme in Italy. Methods: Nivolumab was available upon physician request for pts aged ≥18 years who had relapsed after a minimum of one prior systemic treatment for stage IIB/IIIa/IIIB stage IV Sq-NCSLC. Nivolumab 3 mg/kg was administered intravenously every 2 weeks to a maximum of 24 months. Pts included in the analysis had received at least 1 dose of nivolumab and were monitored for adverse events (AE) using Common Terminology Criteria for Adverse Events. Results: In total, 371 Italian pts participated in the EAP across 96 centres and 3853 patients were evaluable for response. With a median follow-up of 5.2 months (range 0.1-12.9) and a median of 7 doses, the best overall response rate (BORR) was 18%, with 3 complete responses (CR) and 62 partial responses (PR), and the disease control rate (DCR) was 47%. DCR was comparable among pts regardless previous lines of therapy, brain metastasis, age and smoking habits. A non-conventional benefit was observed in 23 (7.6D 6 PR) of 66 pts treated beyond RECIST defined progression. As of April 2016, median progression-free survival and median overall survival were 3.9 (95% CI: 3.2-4.6) and 9.1 (95% CI: 6.7-11.5) months, respectively. Regarding the safety profile, 267 out of 371 pts (72%) had at least one AE of any grade, considered to be drug-related in 106 pts (29%). Grade 3/4 AEs were reported in 66 pts and considered to be drug-related in 20 pts (5%). AE were generally manageable following the specific guidelines. Conclusion: To date, this is the largest clinical experience with nivolumab in a real-world setting. This preliminary EAP data seems to confirm the efficacy and safety data of nivolumab from registrational trials, supporting its use in current clinical practice for pre-treated pts with Sq-NCSCL.

Keywords: Real-word data, Nivolumab, squamous NSCLC.

References:
1. San Gerardo, Monza/Italy, Lo Studio E La Cura Dei Tumori (IRST) IRCCS, Meldola/Italy, Tumori, Milano/Italy, Research Centre, Istituto Tumori "Giovanni Paolo II" Bari, Italy, Bari/Italy, S. Orsola-Malpighi University Hospital, Bologna/Italy, S702
2. Journal of Thoracic Oncology  •  Volume 12 Issue S1 January 2017
3. Abstracts
**Background:** Nivolumab is an immune checkpoint inhibitor antibody that inhibits the programmed cell death protein 1 (PD-1) immune checkpoint. It has demonstrated durable responses and tolerability in patients with pretreated advanced NSCLC. This retrospective study evaluates the efficacy and safety of nivolumab, which was approved for the treatment of advanced NSCLC in December 2015 in Japan. Methods: This study comprised 50 patients with advanced or recurrent NSCLC who were administered with nivolumab 3mg/kg IV every 2 weeks from December 2015 through April 2016 at Mutsukasa Municipal Hospital. Results: Patient demographics were as follows: a median age of 69 years (range: 53–86); 17 females and 33 males; 12 non-smokers and 38 former or current smokers; 47 patients with squamous cell carcinoma, 33 with adenocarcinoma, two with large-cell carcinoma, and 4 NSCLC; 20 stage IIIB and 46 stage IV; 17 with central nervous system metastasis; 30 received 2 or more prior therapy lines and 62 had PS 1. Among 48 patients evaluated, 3% had complete response, 21% partial response, 27% disease stabilization and 21% disease progression. At 62 had PS 1. Among 48 patients evaluated, 3% had complete response, 21% partial response, 27% disease stabilization and 21% disease progression.

**Conclusion:** Early data from this study suggests that Nivolumab is effective and well tolerated in patients with pretreated advanced NSCLC.

**Keywords:** efficacy, anti-PD1, Nivolumab, advanced NSCLC

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**Table 1. Patient characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Elderly group</th>
<th>Poor PS group</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>Median (range)</td>
<td>78 (75–83)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td>Male</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>2</td>
</tr>
<tr>
<td><strong>Histologic type</strong></td>
<td>Adenocarcinoma</td>
<td>10</td>
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<tr>
<td></td>
<td>Squamous cell carcinoma</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>NSCLC</td>
<td>0</td>
</tr>
<tr>
<td><strong>Stage</strong></td>
<td>IIIA</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>IIIB</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>IV</td>
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</tr>
<tr>
<td><strong>Postoperative recurrence</strong></td>
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<td>1</td>
</tr>
<tr>
<td><strong>ECOG PS</strong></td>
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<td>3</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>1</td>
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<tr>
<td><strong>Smoking status</strong></td>
<td>Current or former smoker</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Never smoked</td>
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<td><strong>EGFR mutation status</strong></td>
<td>Exon19</td>
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<tr>
<td></td>
<td>Exon21</td>
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<td><strong>Other systemic treatments</strong></td>
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<td></td>
<td>5</td>
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<tr>
<td><strong>PD-L1 status of tumor</strong></td>
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</tr>
<tr>
<td></td>
<td>Not quantifiable</td>
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<tr>
<td><strong>Response</strong></td>
<td>PR</td>
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<tr>
<td></td>
<td>SD</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>PD</td>
<td>4</td>
</tr>
<tr>
<td><strong>Treatment-related AEs leading to discontinuation</strong></td>
<td>1 (grade 3)</td>
<td>1 (grade 4)</td>
</tr>
<tr>
<td></td>
<td>2 (grade 3)</td>
<td>2 (grade 4)</td>
</tr>
<tr>
<td></td>
<td>3 (grade 3)</td>
<td>3 (grade 4)</td>
</tr>
<tr>
<td><strong>Adverse effect</strong></td>
<td>1 (grade 2)</td>
<td>0 (grade 2)</td>
</tr>
<tr>
<td></td>
<td>1 (grade 1)</td>
<td>0 (grade 1)</td>
</tr>
</tbody>
</table>

*Note: One patient aged 75 had a PS of 2.*

Conclusion: Nivolumab had a clinically meaningful response for elderly or poor PS advanced NSCLC patients, but toxicity led to the discontinuation of nivolumab.

**Keywords:** Advanced Non-Small Cell Lung Cancer, Nivolumab, elderly, poor performance status

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**Poster Session 3 – P3.02c.099 An observational study of the efficacy and safety of Nivolumab in patients with advanced NSCLC. A Galician Lung Cancer Group**

**Rosario García Campelo,** Maria Carmen Areces, Francisco Baron, Francisco Afonso-Afonso, Marína Costa, Natalia Fernandez, Margarita Amenedo, Guillermo Alonso-Jaudenes Curvera, María Vázquez, Rocio Vilchez Simo, Joaquín Mosquera Martinez, Jorge García, Susana Gómez, Begoña Campos, Jesus Garcia Mata, Urbano Anido Herranz, Jose Luis Fivida

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**Background:** Nivolumab is an immune checkpoint inhibitor antibody and it has demonstrated durable responses and tolerability in pretreated patients with advanced NSCLC. This is an observational study to evaluate the efficacy and safety of nivolumab in previously treated patients with advanced NSCLC in the expanded access programme. Methods: Eligibility criteria included, histologically confirmed NSCLC clinical stage IIIIB or IV, evaluable disease, at least one prior chemotherapy, performance status of 0/1 and an adequate organ function. Exclusion criteria included, positive test for hepatitis B, C, or human immunodeficiency virus, severe autoimmune disease and patients with systemic corticosteroids or immunosuppressive medications. Patients received nivolumab 3mg/kg IV (60 min) every 2 weeks until progressive disease (PD) or unacceptable toxicity. The aim of the study was to report the efficacy and safety profile of Nivolumab in pretreated patients with advanced NSCLC of our everyday clinical practice. The exploratory assessments include response rate (RR), progression-free survival (PFS), overall survival (OS) and treatment related adverse events (AEs). Results: From August of 2015 to February of 2016, with a median follow time of 7 months, 66 patients were enrolled from 7 different centers. The patients demographics were: median age 60 years, 19 female and 47 male; 7 never smoked and 59 former or current smoker, 45 patients adenocarcinoma, 4 large-cell carcinoma, 12 squamous-cell carcinoma and 4 NSCLC; 20 stage IIIB and 46 stage IV; 17 with central nervous system metastasis; 30 received 2 or more prior therapy lines and 62 had PS 1. Among 48 patients evaluated, 3% had complete response, 21% partial response, 27% disease stabilization and 21% disease progression. At the time of database lock, the median of PFS was 2.03 IC 95% (1.2-2.7) and OS was not reached.

**Conclusion:** Early data from this study suggests that Nivolumab is effective and well tolerated in patients with pretreated advanced NSCLC.

**Keywords:** efficacy, anti-PD1, Nivolumab, advanced NSCLC

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**Poster Session 3 – P3.02c. Advanced NSCLC & Chemotherapy/Targeted Therapy/Immunotherapy**

**Is Clinical – Wednesday, December 7, 2016**

**P3.02c-099 A RETROSPECTIVE STUDY OF THE EFFICACY AND SAFETY OF NIVOLUMAB IN OUR CLINICAL PRACTICE: A SINGLE INSTITUTIONAL EXPERIENCE**

**Tadashi Sakaguchi,** Osamu Hataki, Yuta Suzuki, Haruko Saiki, Kentaro Ito, Yoichi Nishii, Kosuke Hayashi, Fumiaki Watanabe, Tetsu Kobayashi, Esteban Gabazza, Osamu Taguchi

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**Background:** Nivolumab is a fully humanized, IgG4 antibody that inhibits the programmed cell death protein 1 (PD-1) immune checkpoint. It has demonstrated durable responses and tolerability in patients with treatment resistant, advanced non-small cell lung cancer (NSCLC). This retrospective study evaluates the efficacy and safety of nivolumab, which was approved for the treatment of advanced NSCLC in December 2015 in Japan. Methods: This study comprised 50 patients with advanced or recurrent NSCLC who were administered with nivolumab 3mg/kg IV every 2 weeks from December 2015 through April 2016 at Mutsukasa Municipal Hospital. Results: Patient demographics were as follows: a median age of 69 years (range: 53–86); 17 females and 33 males; 12 non-smokers and 38 former or current smokers; 47 patients with ECOG performance status (PS) of 0 or 1 and three with a PS of 2; seven patients with postoperative recurrence, nine with post-definitive chemoradiotherapy, 31 with stage IV disease, and three with others; 14 patients with squamous cell carcinoma, 33 with adenocarcinoma, two with pleomorphic carcinoma, and one with NSCLC NOS; 17 patients received nivolumab as second-line and 33 patients as third-line therapy or later; and six patients with EGFR mutation and one with ALK rearrangement. Among 50 patients, nine showed partial response, 17 showed stable disease, and 22 showed progressive disease, 2 were not evaluated yet. Five patients experienced an initial increase in the size of their tumors, but with a subsequent decrease in tumor burden. At the time of submission, the median PFS was 3.8 months, with OS yet to be evaluated. Grade 3–4 AEs occurred in seven patients, with Grade 5 AEs occurring in only one patient. Conclusion: Early data from this study suggests that nivolumab is effective and well tolerated in patients with advanced or recurrent NSCLC in a real clinical setting.

**Keywords:** Nivolumab, NSCLC

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**Abstracts**

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**S703**
**P3.02C-100 NIVOLUMAB BEYOND FIRST-LINE (1L) TREATMENT IN METASTATIC NON-SMALL CELL LUNG CANCER (NSCLC)**

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Background: Patients with metastatic NSCLC progressing to 1L have a poor prognosis. Nivolumab is an anti-PD-1 monoclonal antibody, which has shown to prolong overall survival (OS) in patients who have progressed to platinum-based chemotherapy. We report our experience with nivolumab in pretreated metastatic NSCLC patients. Methods: Retrospective study of patients with metastatic NSCLC treated with nivolumab (3 mg/kg every 2 weeks in second line (2L) and subsequent lines (SL)). We evaluate response rate (RR), progression-free survival (PFS), OS and toxicity. Results: Twenty patients were included (2L: 17, SL: 13). Median age: 68 years. Histology: Adenocarcinoma (60%), Squamous cell (33%), Large cell (7%). ECOG PS: EC0G 0-1 (93%), EC0G 2 (7%). Median number of cycles: 8. RR: Twenty-three patients evaluable for response. Complete response (3%), partial response (35%), stable disease (26%), disease progression (33%). Objetive response rate (ORR) in 2L vs SL: 55% vs 33%, p=0.30. ORR in squamous vs non-squamous: 25% vs 47%, p=0.40. Median follow-up: 6 months. PFS and OS events at the time of analysis: 43% and 33%, respectively. Median PFS and OS: 7 months and not reached, respectively. PFS in 2L vs SL: NR vs 5 months, HR 0.81, p=0.71. PFS in squamous vs non-squamous: 5 months vs NR, HR 1.39, p=0.58. OS in 2L vs SL: NR vs NR, HR 1.53, p=0.50. OS in squamous vs non-squamous: 7 months vs NR, HR 2.61, p=0.14. The incidence of adverse events was low. The most frequent toxicity (any grade) was anemia (67%). A patient with chronic liver disease had hepatotoxicity grade 1 and continued treatment. Three patients discontinued treatment due to toxicity: pneumonitis grade 3 (1), rash grade 3 (1), impaired renal function grade 3 (1). There were no toxic deaths. Conclusion: In clinical practice, nivolumab is effective and safe in 2L and SL in patients with metastatic NSCLC.

Keywords: Nivolumab, NSCLC

**P3.02C-101 IMMUNOVUM WITH NIVOLUMAB IN NSCLC PATIENTS: ONE CENTRE PRELIMINARY RESULTS**

Sofia Lampaki, Eftimia Boutsikou, Paul Zargouzidis, Dioniou Sprotas, Elada Eleftheriadou, Despoina Ioannidou, Christoforos Efthimiou, Theodoros Kontokitsi, Konstantinos Zargouzidis

Pulmonary Department, G. Papanikolaou Hospital, Aristotle University of Thessaloniki, Thessaloniki/Greece

Background: Nivolumab is an IgG4 monoclonal antagonist antibody to PD-1 that is approved for the treatment of patients with advanced squamous and non-squamous NSCLC with progression of disease on or after standard platinum-based chemotherapy, regardless of tumor PD-L1 protein expression. The aim of our study is to evaluate the efficacy and safety of nivolumab in this group of patients. Methods: We enrolled 23 patients with squamous and non-squamous NSCLC, stage IIIB/V,19 males and 4 females, with a median age 68 years who had failed two or more lines of systemic platinum based chemotherapy. All patients received at least 4 doses of nivolumab as monotherapy, at a dose of 3 mg/kg once every 2 weeks intravenously, until disease progression or unacceptable toxicity. Results: 3 (13%) of 23 patients had an objective response as assessed by RECIST criteria and all of the responses were ongoing at the time of analysis. 19 (82.6%) of 23 patients had stable disease and one experienced progression of the disease. 2 (9%) of 23 patients reported treatment-related adverse events, including peripheral edema, one (4%) with pleural effusion and one (4%) with periarticular effusion, which all were well tolerated and treated. No deaths were attributed to nivolumab. Conclusion: Nivolumab has clinically meaningful activity and a manageable safety profile in previously treated patients with advanced, resistant, squamous and non squamous non small cell lung cancer.

Keywords: Immunotherapy, Nivolumab, non small cell lung cancer

**P3.02C-102 SAFETY AND TOLERABILITY OF ABEABICILB COMBINED WITH LY3034314 OR WITH PEBMOLZUMAB IN PATIENTS WITH STAGE IV NSCLC**

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Background: Currently, treatment options are limited for patients with advanced and/or metastatic NSCLC particularly after initial treatment. In a prior phase 1 study, abemaciclib, a CDK4/6 inhibitor, demonstrated single-agent anti-tumor activity when dosed orally on a continuous schedule, with an acceptable safety profile in patients with previously treated metastatic NSCLC (NCT01394016). PI3Kα is an escape pathway after CDK inhibition in tumor models and aberrant immunity is a hallmark of cancer, providing the rationale to combine abemaciclib with PI3K and with checkpoint inhibitors. An ongoing Phase 1b multicenter, open-label, 3+3 dose-escalation trial with an expansion phase is investigating abemaciclib in combination with multiple single-agent options in metastatic NSCLC (NCT02079363). Here we report the results of a sub-analysis of patients with advanced NSCLC treated with abemaciclib orally on a continuous schedule every 12 hours (q12h) in combination with the PI3K/mTOR inhibitor, LY3034314, at 100, 150, or 200 mg q12h. In Part E, abemaciclib was administered in combination with the anti-PD-1 antibody, pembrolizumab (200 mg i.V. infusion q3 weeks). Patients with late stage NSCLC and 1-3 prior therapies without central nervous system metastasis were treated until disease progression or other discontinuation criteria were met. Primary endpoints for each cohort included safety/ tolerability and identification of the recommended phase 2 dose. Safety assessments followed the Common Terminology Criteria for Adverse Events (NCI-CTCAE v4.0). Parts D and E began enrolling patients on April 13, 2015 and April 29, 2016, respectively. Results: As of August 24, 2016, Parts D and E escalation included, respectively, 22 (male [64%]/Caucasian [77%]) stage IV (91%)/adenocarcinoma (91%) and 6 patients [male [33%]/Caucasian [100%]/ stage IV (67%)/adenocarcinoma (100%)]. ECOG PS was ≤1 in both cohorts. In Part D, 1 patient on dose level 2 (2L)-2 experienced a dose limiting toxicity (DLT) (Grade 4 thrombocytopenia). Evaluation of additional dose levels is ongoing. Seventeen patients (77%) experienced ≥1 treatment-related adverse event (TRAE). Common TRAEs were nausea (50%), diarrhea (50%), vomiting (36%), fatigue (32%), and decreased appetite (27%). In Part E, no DLTs or deaths occurred in the two dosing cohorts evaluated. Four patients (67%) experienced ≥1 TRAE with 75% Grade 2. Common TRAEs included fatigue (50%), diarrhea and proteinuria, (33%, each). Conclusion: The majority of previously treated advanced/metastatic NSCLC patients administered abemaciclib with LY3034314 or with pembrolizumab with manageable and tolerable adverse events, similar to those of the single agents.

Keywords: CDK4/6, PI3/mTor, PD-1, NSCLC

**P3.02C-103 EFFECT OF ANTI-PD-1 THERAPY ON IMMUNE CELLS IN THE PERIPHERAL BLOOD OF NON-SMALL CELL LUNG CANCER (NSCLC) PATIENTS**

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1Laboratory of Translational Oncology, University of Cote, School of Medicine, Heraklion/Greece, 2Medical Oncology, University Hospital of Heraklion, Heraklion/ Greece

Background: Programmed cell death 1 (PD-1), plays a pivotal role in tumor immune escape. Recently, antibodies targeting PD-1 and PD-L1 have been approved for treatment of advanced Non Small Cell Lung Cancer (NSCLC). In this pilot study, we aimed to investigate the effect of anti-PD1 treatment on the frequencies of circulating PD-1+ T cells and PD-L1+ immunosuppressive cells in NSCLC patients. Methods: Peripheral blood samples were collected from 35 advanced NSCLC patients before initiation of treatment and after 3 cycles. Twelve treatment-naïve patients received...
Moreover, a significant decrease of PD-1+ the percentage of the PD-L1
line chemotherapy (Keywords: immune cells, NSCLC, Anti-PD-1
impact on their clinical relevance in NSCLC patients.
treatment with anti-PD1 agents have an overall positive effect on immune
to anti-PD1 therapy. The frequencies of both peripheral
Moreover, the levels of PD-1 CD4+ (p=0.009) and PD-1 CD8+ (p=0.009) were
increased in response to anti-PD1 therapy. The frequencies of both peripheral
CD4+ Treg (CD3+ CD4+ CD25high/low CD127+/- CD152/FoxP3+) and granulocytic
In contrast, after 3 cycles of chemotherapy, the levels of PD-L1+ T cells
were decreased following anti-PD1 therapy (p=0.01 and p=0.02, respectively).
In contrast, 3 cycles of chemotherapy, the levels of PD-L1+ CD4+ Treg
were increased, but not of the PD-L1+ G-MDSC (p=0.04). Anti-PD1 treatment
significantly reduced the percentages of PD-1+ CD4+ , PD-1+ CD8+ T cells,
PD-L1+ CD4+ Treg and PD-L1+ G-MDSCs when compared to the effect of first
line chemotherapy (p=0.04, p=0.05, p=0.002 and p=0.01, respectively).
Furthermore, a significant decrease of PD-1+ CD8+ T cells, PD-L1+ CD4+ Treg
and PD-L1+ G-MDSCs after 3 doses of anti-PD1 was observed in patients
who experienced stable disease compared to baseline (p=0.006, p=0.05 and
p=0.03, respectively). At the time of response evaluation to chemotherapy,
the percentage of the PD-L1+ CD4- Treg after 3 cycles was significantly
decreased compared to baseline, in disease progressors (p=0.006). Conclusion:
Treatment with anti-PD1 antibodies significantly reduces the levels of PD-1+
effectors cells, as well as the PD-L1- suppressive Treg and G-MDSCs. In contrast
chemotherapy led to an increase of PD-L1+ Treg. These data indicate that
treatment with anti-PD1 agents have an overall positive effect on immune
system by reducing the immunosuppressive cells and increasing the effector
cells. Additional studies are needed in a larger cohort in order to document its
impact on their clinical relevance in NSCLC patients.

Keywords: immune cells, NSCLC, Anti-PD-1

P3.03-001 TARGETING CULLIN UBIQUITIN LIGASE LEADS TO GROWTHS ARREST IN MALIGNANT PLEURAL MESOTHELIOMA CELLS
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Background: Mutation of the tumor suppressor gene NF2 was detected in 30-40% of malignant pleural mesothelioma (MPM) patients. NF2 suppresses tumorigenesis in part by inhibiting Cullin ubiquitin ligase. Cullin4A (CULA4) gene amplification and its’ overexpression has been detected in MPM cell lines and tumors. We hypothesized that cullin4 is a potential treatment target for MPM. Cullin’s activity can be blocked by the inhibition of neddylation, a post-translational modification for cullins. In this study we assessed the efficacy of pevonedistat, an inhibitor of protein neddylation.
Methods: Thirty MPM cell lines and 3 MPM primary cells grown in monolayer (2D) were employed to assess the efficacy of pevonedistat in vitro compared to normal mesothelial cells, using MTT assay. The expression of cullins was assessed by quantitative real time PCR and western blot. Cell cycle was analyzed by flow cytometry. Four cell lines were cultured in multicellular spheroid (3D) format and measured for viability by acid phosphatase assay. Results were analyzed by flow cytometry. Four cell lines were cultured in multicellular spheroid (3D) format and measured for viability by acid phosphatase assay. Results: In several cell lines overexpressing CULA4 are highly sensitive to pevonedistat. The treatment with pevonedistat of 3D cell line resulted in accumulation of cells containing S4N DNA content, representing cells undergoing DNA re-replication. DNA re-replication is known to be mediated by the accumulation of a DNA replication licensing factor, CDT1. Indeed, higher CDT1 accumulation was detected in the sensitive compared to the resistant cell lines. All primary cells showed no CULA4 overexpression compared to normal mesothelial cells, nonetheless 2 of them were sensitive to pevonedistat. Interestingly, these cells exhibited higher levels of neddylated (activated) CULA4 and higher CDT1 accumulation following the treatment. Cells lines overexpressing CULA4 remained sensitive to pevonedistat when grown in 2D spheroids.

Conclusion: Inhibition of cullins by pevonedistat induced growth arrest preferentially in MPM cell lines overexpressing CULA4 in 2D and 3D cultures. The major mechanism seems to be mediated by DNA re-replication induced by CDT1 accumulation.

Keywords: cullins, pevonedistat, neddylation, malignant pleural mesothelioma

P3.03-002 INDUCIBLE CHANGES IN CELL MORPHOLOGY AND GENE EXPRESSION RELECTING THE HISTOLOGICAL SUBTYPES OF MESOTHELIOMA
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Background: Malignant pleural mesothelioma (MPM) represents an aggressive malignancy with dismal prognosis and limited therapeutic options. MPM occurs in three main histological subtypes: epithelioid, sarcomatoid and biphasic, which are characterized by differences in morphological growth pattern, aggressiveness and patient prognosis. However, the mechanisms and causes responsible for the different cell morphologies are poorly understood. Epithelial-mesenchymal transition (EMT) has been implicated in cancer progression and chemoresistance, but its role in MPM is not well understood. Fibroblast growth factor receptor (FGFR) signals promote cell growth, survival and aggressiveness in several tumors including mesothelioma. Aim of this study was to characterize growth factor-induced, EMT-like changes with respect to the MPM histological subtypes. Methods: Morphological and behavioral changes of treated cell models were analyzed by morphometry, immunoblotting and functional assays. Alterations in gene or microRNA expression were evaluated via qPCR and array hybridization. Pathway enrichment analysis was based on KEGG. Results: In several cell lines established from biphasic MPM, treatment with FGFR2 and EGF induced morphological changes reminiscent of EMT and aggressive behavior such as scattering, increased migration, proliferation and invasiveness. Inhibition of the fibroblast growth factor receptors (FGFR) or the MAPK axis via small-molecule inhibitors could prevent these changes and, in cell lines with sarcomatoid-like shape, reverse scattering and induce a more epithelioid morphology. Comparable results were observed using an engineered FGFR1 enabling contactless activation via blue light. Analyses of genes and microRNAs regulated by FGFR2 or EGF showed an overlap with previously established EMT markers but also identified several novel potential markers such as MMP1, ESM1, ETF4, PD1, ITG65 and BDKRB2. Blocking the FGFR or
Abstracts

MAPK pathways resulted in the opposite regulation of these genes. Inhibition of MMP1 via siRNAs or pharmacological inhibitors prevented FGFR2-induced scattering and invasiveness. In unsupervised clustering, the gene expression profiles of solvent- or cytokine-treated cells were associated with those of epithelialoid and sarcomatoid MPM, respectively. Immunohistochemistry showed the expression of MMP1 as well as phospho-ERK with the sarcomatoid part of tissue specimens from biphasic tumors. Pathway enrichment analysis of differentially expressed genes as well as the targets of altered microRNAs after FGFR2 treatment showed that the regulated genes are assigned to categories important for cell growth and aggressive behavior. Conclusion: Our data characterize FGFR-mediated signals as important players in MPM aggressiveness and the morphological and behavioral plasticity of mesothelioma cells, leading to a better understanding of the link between the MPM histological subtypes and their influence on patient outcome.

Keywords: Epidermal Mesenchymal Transition, Mesothelioma, Fibroblast Growth Factors

Poster Session 3 - P3.03: Mesothelioma/Thymic Malignancies/Esophageal Cancer/Other Thoracic Mesothelioma Transitional - Wednesday, December 7, 2016

P3.03-003 MesotheLium Covering Pleural Plaque is Not Primarily Involved in Asbestos-Induced MesoThelial Carcinogenesis in Human

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Background: Malignant pleural mesothelioma (MPM) initially arises not from the visceral pleura but parietal pleural mesothelial cells in the thoracic cavity. MPM has a close relationship to asbestos exposure in etiology. The carcinogenic potential of asbestos fibers has been linked to their geometry, size, and chemical composition. Long respirable fibers (length>5μm, diameter<3μm) have an increased potential to cause mesothelioma. Asbestos also induces non-neoplastic diseases of the pleura. Pleural plaques are thought to be formed by lymphatic transport of short asbestos fibers from lung parenchyma to lymphatic stoma in the parietal pleura, with the fibers undergoing phagocytosis by macrophages in the submesothelial layer to synthesize collagen. Long fibers are lodged and retained at these stoma orifices to lead to asbestos carcinogenesis. Plaques, almost always, are produced in the parietal pleura, of which surface is covered with a single mesothelial cell layer. In this study, we evaluated whether mesothelioma covering pleural plaque was primarily involved in asbestos-induced mesothelial carcinogenesis in human.

Methods: 40 patients with MPM were recruited to undergo thoracoscopic biopsy with narrow band imaging (NBI) and autofluorescence imaging (AFI). In addition to white light under local anesthesia, 10 patients were T1, and 8 were T2 clinical stage. All patients had a history of asbestos exposure (e.g., occupational exposure, 7 environmental asbestos). Results: Small nodules of mesothelioma and plaques were present simultaneously on the parietal pleura in 15 MPM patients. NBI could demonstrate with NBI. With progression of the clinical stage of MPM, plaques were smooth surfaced or composed of small rounded knobs. S706

P3.03-004 Genome-Wide Copy Number Aberrations in Mesothelioma and its Correlation with Tumour Microenvironment including PD-L1 expression


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Background: Recent clinical studies have demonstrated positive correlation between tumour mutational burden and response to immune checkpoint inhibitors (ICI) in several malignancies. Although initial reports of some ICI in Malignant Mesothelioma (MM) have shown promising results, the role of somatic mutations in MM is known to be low and copy number aberrations (CNA) are thought to be not significant alter cell of malignant tumors. Herein, we investigated CNA, PD-L1 expression and the surrounding immune infiltrates and correlated these parameters to clinical-pathological features.

Methods: Tissue microarrays (TMA) were constructed and stained with PD-L1 (E1L3N,CST, Massachusetts), CD4, CD8 and FoxP3 antibodies. PD-L1 positivity (PD-L1+) was defined as >5% membranous staining regardless of intensity and high positive as >50%. Genomic DNA was obtained from tumour cores of a representative subset (100 patients) and used for genome-wide copy number analysis. Percent genome aberrated (PGA) was computed for each sample as the total number of base pairs within altered regions, divided by the total number of base pairs in each sample. Coherence of CNA profile and individual aberration (loss/gain) frequency with parameters including PD-L1 expression and survival were explored. Results: Amongst 329 patients evaluated, the median age was 67 years and most were male (72%). 3.2% (9/283) Epithelioid histology (N=203, 62.9%) was the commonest. PD-L1 positivity was seen in 41% with high positivity in 9.6%. PD-L1 correlated with non–epithelioid histology (P<0.0001) and increased infiltration with CD4, CD8 and FoxP3 lymphocytes. High PD-L1 expression correlated with worse prognosis (HR=2.37, 95% CI: 1.75-3.16; P<0.0001) on univariate analysis but the effect was found to be time dependent. Neither PGA (P=0.57) nor CNA profile (P=0.76) were found to be associated with PD-L1 expression. After correction for multiple testing, no individual CNA count was significantly associated with PD-L1 status. Although epithelioid histology had higher PGA (P=0.04), high PGA was associated with poorer survival (HR=2.2, 95% CI: 1.24-3.9 and P=0.004). This was also true when only epithelioid tumours were considered. Conclusion: Increased genomic alterations in MM did not correlate with PD-L1 expression but was associated with poorer survival. High PD-L1 expression was associated with non-epithelioid MM, poor clinical outcome and increased inflammatory infiltrates.

Keywords: Copy number aberrations, PD-L1, Mesothelioma, Tumour infiltrating lymphocytes

Poster Session 3 - P3.03: Mesothelioma/Thymic Malignancies/Esophageal Cancer/Other Thoracic Mesothelioma Transitional - Wednesday, December 7, 2016

P3.03-005 Inhibition of PRMT5 is Synthetic Lethal in Mesotheliomas Harboring MTAP Loss

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Background: Mesothelioma remains an incurable cancer with limited therapy. Genetically targeted personalised treatment strategies are currently lacking. Mesothelioma harbours frequent loss of chromosome 9q21.3 locus encoding for CDKN2A and CDKN2B and tetracopeptide repeat phosphatase 12 (MTRF1). Loss of MTAP has recently been shown to be associated with dependency on the symmetrical demethylation of arginine-4 on histone H4 methyltransferase PRMT5. We sought to determine whether mesothelioma cells with MTAP HD would be vulnerable to inhibition of PRMT5, and to explore the pharmacodynamics associated with its suppression. Methods: Genome-wide copy number variation (CNV) analysis was undertaken in 94 patients. CNVs were determined using the array based platform, Affymetrix Oncoscan v2. Multiregional whole exome sequencing was also performed on samples from 6 patients. The expression of MTAP and the effect of the drugs tested on H4R3Me2s was evaluated by western blot. Cell growth was analysed by clonogenic assay after focused RNAi targeting
Background: Growth factor receptors are central elements of signal transduction pathways and increasingly important targets for anticancer drugs. In recent years naturally occurring light sensitive protein domains (LSPDs) from different kingdoms of life have been used to generate genetically encoded chimeric signalling molecules that can be activated reversibly and with spatiotemporal precision by light. The development of such optogenetic tools has led to a plethora of new discoveries in the neurosciences but has received comparably little attention in cancer research - partly due to a lack of appropriate tools. Our aim was therefore to generate synthetic growth factor receptors that can be activated with light and allow fine-tuned control of growth factor associated signal transduction pathways. Methods: To generate receptor tyrosine kinases (RTKs) that can be optically activated (Opto-RTKs), intracellular domains of RTKs were fused to LSPDs of the light-oxygen voltage (LOV) family from various species. The structure of the spheroids was confirmed by conventional and scanning electron microscopy. MicroRNA expression was profiled using TaqMan ddPCR. Results: Three of the tested LOV domains enabled signal transduction by reporter gene assays, immunoblotting and various cell number variation (CNV) was investigated by ddPCR. Cells were transfected with miR-137 mimic and subsequent YB-1 expression was investigated using RT-qPCR. Proliferation, colony formation and wound-healing assays were conducted after transfection with miR-137 mimics or YB-1-specific siRNAs. Results: miR-137 was absent in 4 MPM cell lines (p<0.01) and was up-regulated in the majority of MPM cell lines, compared to MeT SA. YB-1 knock-down resulted in dose-dependent growth inhibition over 120 hours, reduced colony formation and also decreased cell migration. Effects were more pronounced in those cell lines showing high YB-1 protein levels. Conclusion: Our results show that methylation and CNV are likely to play a role in miR-137 down-regulation in MPM and that miR-137 acts as a tumour suppressor in MPM through at least in part the down-regulation of YB-1. We also demonstrated that YB-1 is commonly overexpressed and plays a role in proliferation and malignant behaviour. Methods: Basal expression of miR-137 and YB-1 was determined in 5 cell lines and gain was present in 2. Increasing levels of miR-137 generally inhibited MPM cell migration, proliferation and colony formation. miR-137 mimics significantly down-regulated YB-1 expression, while YB-1 protein was overexpressed in the majority of MPM cell lines, compared to MeT SA. YB-1 knock-down resulted in dose-dependent growth inhibition over 120 hours, reduced colony formation and also decreased cell migration. Effects were more pronounced in those cell lines showing high YB-1 protein levels. Conclusion: Our results show that methylation and CNV are likely to play a role in miR-137 down-regulation in MPM and that miR-137 acts as a tumour suppressor in MPM through at least in part the down-regulation of YB-1. We also demonstrated that YB-1 is commonly overexpressed and plays a role in proliferation and migration. These results imply a direct relationship between miR-137 and YB-1 expression, a biological interaction that may prove a useful target in developing future therapeutic approaches in MPM.

Keywords: translational research, YB-1, microRNA, Mesothelioma

P3.03-006 OPTICAL CONTROL OF GROWTH FACTOR RECEPTORS TO ADVANCE SIGNAL TRANSDUCTION RESEARCH AND DRUG SCREENING

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Background: Growth factor receptors are central elements of signal transduction pathways and increasingly important targets for anticancer drugs. In recent years naturally occurring light sensitive protein domains (LSPDs) from different kingdoms of life have been used to generate genetically encoded chimeric signalling molecules that can be activated reversibly and with spatiotemporal precision by light. The development of such optogenetic tools has led to a plethora of new discoveries in the neurosciences but has received comparably little attention in cancer research - partly due to a lack of appropriate tools. Our aim was therefore to generate synthetic growth factor receptors that can be activated with light and allow fine-tuned control of growth factor associated signal transduction pathways. Methods: To generate receptor tyrosine kinases (RTKs) that can be optically activated (Opto-RTKs), intracellular domains of RTKs were fused to LSPDs of the light-oxygen voltage (LOV) family from various species. The resulting chimeric receptors were tested for light-dependent activation of signal transduction by reporter gene assays, immunoblotting and various cell biological tests assessing DNA synthesis, epithelial mesenchymal transition (EMT) and angiogenesis. Results: Three of the tested LOV domains enabled light-dependent receptor dimerisation and activation of the corresponding signal transduction pathways when fused to the intracellular domains of FGFR1, EGFR, RET, c-Met or ROS1. Opto-RTKs enabled stringent control of the MAPK, PI3K and PLCγ pathways. Signal activation could be spatially confined to illuminated regions of culture plates and signals rapidly subsided after cessation of illumination. Light was able to replace FGFR for the induction of cell proliferation and EMT in mesothelioma cells and VEGF for the stimulation of angiogenic sprouting in endothelial cells. Moreover, Opto-RTKs enabled light-assisted screening for small molecule inhibitors of EGFR, FGFR1 and the orphan RTK ROS1. Conclusion: Our optogenetic approach allows light-mediated control of growth factor receptors representing clinically relevant drug targets. Opto-RTKs enable dissection of dynamic signals with increased spatiotemporal resolution and open new possibilities for drug screening. Transfer of the design principle to additional membrane receptors is ongoing.

Keywords: receptor tyrosine kinase, drug screening, malignant pleural mesothelioma

P3.03-007 MIR-137 ACTS AS A TUMOUR SUPPRESSOR VIA THE DOWN-REGULATION OF YB-1 IN MALIGNANT PLEURAL MESOTHELIOMA

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Background: Malignant pleural mesothelioma (MPM) continues to increase in incidence worldwide and has limited therapeutic options. MPM displays characteristic changes in gene expression, including noncoding RNAs such as microRNAs, which have potential therapeutic relevance. One such miRNA is miR-137, a tumour suppressor whose promoter region is frequently methylated in other cancers and lies in a commonly deleted chromosomal region in MPM (1p21-23). A potential role for miR-137 in MPM has been suggested by a recent study investigating the causes of miR-137 suppression, the relationship between miR-137 and YB-1, one of its target genes, as well as their roles in MPM cell growth and malignant behaviour. Methods: Basal expression of miR-137 and YB-1 was determined in 13 MPM cell lines by RT-qPCR and immunoblotting. Cells were treated with 5′aza-cytidine and RT-qPCR was conducted to link methylation with miR-137 suppression. Copy number variation (CNV) was investigated by ddPCR. Cells were transfected with miR-137 mimic and subsequent YB-1 expression was investigated using RT-qPCR. Proliferation, colony formation and wound-healing assays were conducted after transfection with miR-137 mimics or YB-1-specific siRNAs. Results: miR-137 was absent in 4 MPM cell lines (p<0.01) and was up-regulated in response to 5′aza-cytidine treatment in these lines, as well as other lines with low basal expression. Copy-number loss was evident in 5 cell lines and gain was present in 2. Increasing levels of miR-137 generally inhibited MPM cell migration, proliferation and colony formation. miR-137 mimics significantly down-regulated YB-1 expression, while YB-1 protein was overexpressed in the majority of MPM cell lines, compared to MeT SA. YB-1 knock-down resulted in dose-dependent growth inhibition over 120 hours, reduced colony formation and also decreased cell migration. Effects were more pronounced in those cell lines showing high YB-1 protein levels. Conclusion: Our results show that methylation and CNV are likely to play a role in miR-137 down-regulation in MPM and that miR-137 acts as a tumour suppressor in MPM through at least in part the down-regulation of YB-1. We also demonstrated that YB-1 is commonly overexpressed and plays a role in proliferation and migration. These results imply a direct relationship between miR-137 and YB-1 expression, a biological interaction that may prove a useful target in developing future therapeutic approaches in MPM.

Keywords: copy number variation, MPM, Pleural mesothelioma, PRMT5

P3.03-008 HYPOXIA-INDUCED CHANGES IN MICRONNA LEVELS CONTRIBUTE TO DRUG RESISTANCE IN A 3D MODEL OF MALIGNANT PLEURAL MESOTHELIOMA

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Background: Malignant pleural mesothelioma (MPM) is an aggressive asbestos-related thoracic cancer. Chemotherapy is the most frequent treatment option but almost every patient will be confronted with recurrence of disease and drug resistance. Previous studies have used 3D spherical cultures to investigate drug response in MPM. We showed that microRNAs are important players in MPM biology and that they contribute to the response of MPM cells to some therapeutic drugs. In the current study we aimed to investigate the role of microRNAs in the drug resistance of a 3D spheroid model of MPM. Methods: MPM cells were grown in standard 2D culture or as 3D spheroids in low adherence round bottom multi-well plates. The structure of the spheroids was confirmed by conventional and scanning electron microscopy. MicroRNA expression was profiled using TaqMan Low Density Arrays. RT-qPCR and droplet digital PCR were used to validate
candidate microRNAs. HIF1a expression was examined in MPM spheres using immunofluorescence staining. Drug cytotoxicity was investigated in both 2D and 3D cultures using standard proliferation assays, and the effect of drugs on gene expression was analysed. MicroRNA mimics and siRNAs were used to determine the influence of microRNA and HIF1a expression on drug resistance. Results: In our adapted model of 3D cell growth, MPM cell lines formed spherical 3D structures, in contrast to the donut shapes reported with other models. MPM cells in these spheroids were more resistant to cisplatin and gemcitabine than when compared to cells grown in 2D cultures. Immunofluorescence revealed a hypoxic gradient with high HIF1a expression observed in the centre of the spheroids. Spheroids also exhibited a significant up-regulation of miR-210, miR-21, miR-378a, miR-195 and miR-146a, and down-regulation of miR-320b and miR-1225b. Transflecting MPM cells in 2D culture with miR-20a or miR-21 mimics resulted in increased drug resistance, whereas HIF1a knockdown inhibited spheroid formation and decreased drug resistance. Spheroids displayed higher expression of the ABCG2 drug pump, and ABCG2 was also up-regulated in cisplatin and gemcitabine treated MPM cells. Conclusion: Our spheroid model revealed a clear impact of hypoxia on gene expression in MPM cells. HIF1a was highly expressed in the hypoxic centre of the spheroids and is an upstream regulator of the microRNAs we found to be differentially expressed. Pharmacologic and genetic modulation of microRNA and HIF1a levels altered drug resistance in MPM cells, suggesting a link between hypoxia, microRNAs and drug resistance in MPM.

Keywords: Mesothelioma, microRNA, drug resistance, Hypoxia

POSTER SESSION 3 – P3.03: MESOTHELIOMA/THYMIC MALIGNANCIES/ESOPHAGEAL CANCER/OTHER THORACIC MESOTHELIOMA TRANSITIONAL – WEDNESDAY, DECEMBER 7, 2016

P3.03-009 ROLE OF MICRONAS AS BIOMARKERS OF MALIGNANT MESOTHELIOMA IN PATIENTS WITH PLEURAL EFFUSION

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Background: Pleural effusion (PE) is a common clinical presentation of a large number of different diseases including malignant pleural mesothelioma (MPM). The approach to patients with PE is not simple and pre-operative cytological examinations or even intra-operative frozen sections are often unhelpful in the differential diagnosis. This fact makes critical the identification of PE related to MPM and PE of patients affected by other pleural diseases. We aimed to determine whether a miRNA signature in plasma or in Exhaled Breath Condensate (EBC) may help to discriminate between PE related to MPM and PE of patients affected by other pleural diseases (NM). Methods: We prospectively enrolled consecutive patients with PE from suspected MPM, scheduled for thoracoscopic pleural biopsy. We measured clinical data and computed histological diagnosis. Exclusion criteria were age <18 years, history of previous tumor or immunological disorder. Ethics committee approval was achieved. Written informed consent was obtained from all participants. We collected a sample of plasma and EBC from each patient before the biopsy. We screened 733 microRNAs in blood and EBC by high-throughput Open Array and compared their expression in the two groups. We used a multiple linear regression model adjusted for four principal variables (age, sex, BMI and smoking habits) to compare MPM and NM. Results: We enrolled 32 patients; the figure below shows main clinical data.

Malignant Pleural / Mesothelioma Non-Mesothelioma

<table>
<thead>
<tr>
<th>Histology</th>
<th>Malignant Pleural / Mesothelioma</th>
<th>Non-Mesothelioma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sar, male n (%)</td>
<td>17 (73.9)</td>
<td>7 (88.3)</td>
</tr>
<tr>
<td>Age, average (SD) [years]</td>
<td>70.2 (7.8)</td>
<td>72.3 (7.4)</td>
</tr>
<tr>
<td>Body Mass Index, average (SD)</td>
<td>25.1 (4.4)</td>
<td>26.7 (6.7)</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>6 (26.1)</td>
<td>2 (22.2)</td>
</tr>
<tr>
<td>Active or former</td>
<td>12 (52.1)</td>
<td>5 (55.6)</td>
</tr>
</tbody>
</table>

After microRNA screening, we identified 3 microRNAs which were upregulated in EBC and 44 in plasma. In particular, in EBC, miR-378, miR-206, miR-9 with fold-change (FC) of 1.54, 1.4, 1.23 respectively (p-values 0.019, 0.04 and 0.04 respectively) and the most significant in plasma was miR-489 (FC=1.35, p-value=0.0001). Conclusion: We identified a microRNA panel that might be useful for developing a non-invasive procedure for MPM diagnosis in patients with PE.

Keywords: microRNA, exhaled breath condensate, pleural effusion, malignant pleural mesothelioma

POSTER SESSION 3 – P3.03: MESOTHELIOMA/THYMIC MALIGNANCIES/ESOPHAGEAL CANCER/OTHER THORACIC MESOTHELIOMA TRANSITIONAL – WEDNESDAY, DECEMBER 7, 2016

P3.03-010 ACTIVATION OF P53 IN MALIGNANT MESOTHELIOMA

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Background: Certain microRNA (miRNA)-mRNA interactions are associated with critical biologic processes in malignant pleural mesothelioma (MPM). We wondered how microRNA interact with p53 in MPM since this tumor characteristically retains its p53 protein and its transcriptional activity is frequently suppressed by deletion of CDKN2A. This interaction among miRNA and p53 in MPM is poorly understood. Study of this interaction could provide insights on disease mechanisms and/or novel therapeutic strategies. Methods: We retrieved several public miRNA expression MPM data sets to perform a broad survey. We combined two meta-analyses approaches to the normalized data to maximize identifying altered microRNA specific to MPM. Then miRNAs were fit into a network where they inhibited MM2D, releasing inhibition of p53, and in turn were themselves induced by p53 (p53 regulation via a reinforcing loop). Significant microRNA of this screening algorithm were confirmed by qPCR analysis in MPM tissues and cell lines. Specific miRNAs were re-expressed in MPM cells by a lentivirus system or by mimic transfection. p53-luciferase reporter system was used to assess p53 activity. MTS assay assessed cell proliferation. Apoptotic cells were detected by Annexin V assay. Tumorigenic characteristics of MPM cells were evaluated by clonogenicity, soft agar colony formation and 3D assay. Cellular relevance of these miRNAs were assessed in the TCGA MPM cohort (cancergenome.nih.gov). Results: Our meta-analysis, revealed significant changes in several p53-regulated miRNAs. For example, miR-145 expression is repressed by 40% at steady state in MPM specimens (n=38) compared to non-malignant controls (n=21). We directly confirmed in MPM tissues a similar trend of this miRNA, while MM2D miRNA levels were inversely higher. Next, we assessed the functional role of miR-145 in MPM cell lines with wild-type p53. Using a lentiviral expression system to sustain elevations in miR-145 levels, MM2D transcript and protein levels were repressed, leading to increased p53 protein and its transcriptional activity. We observed in miR-145-overexpressed MPM cell lines more apoptosis by Annexin V assay, loss of clonogenicity, growth inhibition, and attenuated tumorigenicity. To confirm that p53 can perpetuate a positive reinforcing loop inducing miR-145, we treated a panel of MPM cells with Nutlin-3a and observed coordinated increases in p53 associated with a rise in miR-145 levels. Interestingly, at least one of these miRNA was prognostic in Kaplan-Meier modeling of overall survival. Conclusion: We have identified candidate microRNAs that, in part, regulate p53 activity in MPM cells. These microRNAs function as tumor suppressors. They are candidates for therapeutic validation.

Keywords: Mesothelioma, p53, tumor suppressor
Background: to investigate whether there was any relationship between survival and the expression of tumor infiltrating lymphocytes (TILs), programmed cell-death ligand-1 (PD-L1), BAP-1 (BRCA1-Associated Protein 1), VEGFR-2 (vascular endothelial growth factor receptor 2) and IGF-1R (Insulin-Like Growth Factor 1 Receptor) in malignant pleural mesothelioma (MPM). Methods: 63 cases of MPM were identified. All tissues were obtained at the time of diagnosis. There were 40 males; mean age was 70.4 years. 34 patients were smokers and 40 had a certain history of asbestos exposure.

Conclusion: Downregulation of miR-30d is related to malignant mesothelioma and asbestos exposure. miR-30d might be a tumor-suppressor miRNA, and its down-regulation might contribute to pleural MM progression and asbestos carcinogenesis.

Keywords: Mesothelioma, neoplasm invasiveness, microRNA-30d (miR-30d), asbestos exposure.

POSTER SESSION 3 - P3.03: MESOTHELIOMA/THYMIC MALIGNANCIES/ESOPHAGEAL CANCER/OTHER THORACIC
MESOTHELIOMA TRANSITIONAL - WEDNESDAY, DECEMBER 7, 2016

P3.03-012 TUMOR-INFILTRATING LYMPHOCYTES, PD-L1, BAP-1, VEGFR-2 AND IGF-1R EXPRESSION IN MALIGNANT PLEURAL MESOTHELIOMA

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Abstracts

Background: to investigate whether there was any relationship between survival and the expression of tumor infiltrating lymphocytes (TILs), programmed cell-death ligand-1 (PD-L1), BAP-1 (BRCA1-Associated Protein 1), VEGFR-2 (vascular endothelial growth factor receptor 2) and IGF-1R (Insulin-Like Growth Factor 1 Receptor) in malignant pleural mesothelioma (MPM). Methods: 63 cases of MPM were identified. All tissues were obtained at the time of diagnosis. There were 40 males; mean age was 70.4 years. 34 patients were smokers and 40 had a certain history of asbestos exposure. All histological slides were revised; there were 30 epithelioid subtypes, 20 biphasics and 13 sarcomatoids. The presence of TILs was scored as absent, weak, moderate and strong according to a quantitative assessment on hematoxylin and eosin slides. The expression of BAP-1, VEGFR-2, PD-L1 and IGF-1R was analyzed by immunohistochemistry. The impact of asbestos exposure, tobacco consumption and histological subtypes on survival were also assessed. The survival analysis was analyzed by Kaplan Meier curve. Results: TILs were present in 89% of cases and were found to be a favorable prognostic factor (p=0.009) although related with histological subtypes (p=0.008). The absence of TILs was higher in biphasic and sarcomatoid subtypes (90.9%, 30/33) compared to epithelioid MPM (53.3%, 16/30 p<0.001). Median survival in TILs and non-TILs patients was 28 months and 11 months, respectively. The expression of PD-L1 in tumor cells (cut-off: 10%, p=0.028) and VEGFR-2 in TILs (p=0.003) were related with survival, but they were differently expressed in histological subtypes. Using a logistic regression model, TILs, PD-L1 and VEGFR-2 in TILs correctly classified 21/30 epithelioid subtypes (70%) and 25/33 biphasic and sarcomatoid subtypes (79%). IGF-1R was overexpressed in 82% of the tumors (21 epithelioids and 31 sarcomatoids) and in 25% of TILs (7 epithelioids and 3 sarcomatoids) and was a favorable prognostic factor (p=0.023) independently of the histological subtype. Median survival was 4 and 13 months in patients not overexpressing and overexpressing IGF-1R, respectively. In a Cox regression model including both IGF-1R and histological subtype, IGF-1R remained significant (p=0.006, HR=0.41 [0.20-0.84]). Tobacco, asbestos exposure, age and BAP-1 expression were not significantly related with survival. Conclusion: the histological subtype is an important prognostic factor in MPM and it’s related to different histological markers: the presence of TILs, PD-L1 and VEGFR-2 in TILs. Moreover, the overexpression of IGF-1R is an independent favorable prognostic factor. Therefore, histological markers may improve the prognostic assessment of MPM and provide mechanistic clues for new therapeutic strategies.

Keywords: malignant pleural mesothelioma, Biomarkers
Background: Distinction between mesothelioma and reactive mesothelial proliferation is difficult because of morphological overlap between mesothelioma cells and reactive mesothelial cells. It is often difficult to draw the line between epithelioid mesothelioma and biphasic mesothelioma with atypical Stromal proliferation. However, separation of biphasic mesothelioma from epithelioid mesothelioma is important because therapeutic option and prognosis is different between two subtypes of mesothelioma. Methods: We collected 143 cases with malignant mesotheliomas (83 epithelioid, 22 biphasic and 38 sarcomatoid) and 33 cases with reactive mesothelial proliferation. Immunostaining was performed with anti-BAP1 antibody. Fluorescence in situ hybridization (FISH) analysis was performed with BAP1 probe and with p16 probe. BAP1 loss and deletion of p16 was separately analyzed in 19 biphasic mesotheliomas. Results: We analyzed 76 cases with BAP1 immunostaining, 87 cases with p16 FISH, and 37 cases with BAP1 FISH. BAP1 loss with immunohistochemistry was observed in 55% of epithelioid and 37% of biphasic mesotheliomas, but not in sarcomatoid mesotheliomas. Homozygous deletion (HD) of BAP1 was observed in 50% of epithelioid and 11% of biphasic mesotheliomas, but not in sarcomatoid mesotheliomas. Homozygous deletion (HD) of BAP1 was observed in 50% of epithelioid mesotheliomas, but not in sarcomatoid mesotheliomas. HD of p16 was observed in 64% of epithelioid, 91% of biphasic, and 100% of sarcomatoid mesotheliomas. Concordance of BAP1 loss and HD of p16 between epithelioid and sarcomatoid components of 19 biphasic mesotheliomas was 100%. Four of epithelioid mesotheliomas were difficult to differentiate from biphasic mesothelioma with histology alone because of florid proliferation of atypical Stromal cells; however, BAP1 loss and HD of p16 were observed in atypical Stromal proliferation and diagnosis of epithelioid mesothelioma could be made. There was a significant difference in overall survival according to histologic subtype (epithelioid 24M, biphasic 15M, sarcomatoid 4.5M). Mesotheliomas with loss of BAP1 expression showed increased survival (20M vs 8M) and HD of p16 showed poor survival (9.5M vs 28M). However, if only epithelioid cases were analyzed, there was no trend toward increased survival with BAP1 loss (24M vs 22M) while HD of p16 still showed poor survival (17M vs 28M). Conclusion: Most of biphasic mesotheliomas and all sarcomatoid mesotheliomas harbor HD of p16. BAP1 loss and HD of BAP1 are observed in epithelioid and biphasic mesotheliomas, but not in sarcomatoid mesotheliomas. BAP1 immunostaining and FISH analysis of p16 help making distinction between epithelioid and biphasic mesothelioma as well as between benign and malignant mesothelial proliferation. p16 is a prognostic factor for patients with epithelioid mesothelioma, but BAP1 is not.

Keywords: p16, Mesothelioma, BAP1, Prognosis

Background: Breast cancer type 1 susceptibility associated protein (BAP1) is a deubiquitinating hydrolase that plays a key role in various cellular processes and acts as a tumor suppressor gene. Malignant mesothelioma is a deadly disease strongly associated with asbestos exposure. Most of the cases (70%) are pleural mesotheliomas while peritoneal and pericardial mesotheliomas account for 25% and 5%, respectively. Germline and somatic inactivation of BAP1 has been recurrently reported in pleural mesothelioma. However, due to its rarity and challenging diagnosis, little is known about the BAP1 status in peritoneal mesothelioma, with the largest series so far including only 12 tumors. Methods: Taking advantage of the extensive French national networks MESOPATH and RENAPE, we collected biological material and clinical and epidemiological data for 46 peritoneal mesothelioma patients. In order to determine the status of BAP1 in these samples, three different levels were evaluated: copy number changes by comparative genomic hybridization arrays (Chirac et al., Human Path 2016), mutations by next-generation sequencing, and protein expression by immunohistochemistry. Results: We detected copy number losses, mutations, and/or loss of expression of BAP1 in 42.2%, 33.3%, and 56.8% of the malignant peritoneal mesotheliomas analyzed, respectively. In most cases with available data (13/16), the loss of BAP1 expression was explained by co-occurring copy number loss and/or mutation. Overall, 73.2% of the malignant peritoneal mesotheliomas analyzed carried an inactivated BAP1 gene. In addition, BAP1 mutations were exclusively detected in males and a better overall survival was observed for patients with loss of BAP1 expression independent of age, sex, smoking and asbestos exposures (p=0.03). Conclusion: Inactivation of BAP1 seems to have a key role in the development of both pleural and peritoneal mesotheliomas. In addition, we found that loss of BAP1 expression in peritoneal mesotheliomas was mostly explained by copy number losses and mutations, and was associated with a better overall survival.

Keywords: Peritoneal mesothelioma, BAP1, Mesothelioma, asbestos
Background: Mutations in the genes cyclin-dependent kinase inhibitor 2A (CDKN2A), BRCA-1 associated protein 1 (BAP1), and neurofibromatosis type 2 (NF2) are observed in malignant pleural mesothelioma (MPM). We observed biallelic BAP1 alterations in 61% of MPMs and found that mutations are particularly frequent in epithelioid-type malignant mesothelioma (Cancer Sci, 103:868-74, 2012). In addition, loss-of-function mutations in NF2 are relatively frequent (40%) in MPMs. We observed merlin in tumor tissue from 31 patients (n=31), 20 with epithelial and 11 with non-epithelial tumors. Merlin is a tumor suppressor protein that is associated with suppression of invasion and metastasis of tumor cells. In this study, we examined the association between loss-of-function mutations in the tumor suppressor gene merlin and the tumor properties of MPM. Methods: Following definitive histological diagnoses of 35 cases of MPM (epithelial: n=31, biphasic: n=2, desmoplastic: n=2), we conducted immunochemical staining for merlin in thin sections of paraffin-embedded tumor tissue. Stainability was assessed with H-scores. The clinical stage of MPM was defined at the time of surgery. The association between clinical and histopathological features was assessed based on the outcomes of first-line chemotherapy with cisplatin (CBDCA) plus pemetrexed (PEM). Results: 1) Seven MPMs (20%) were negative or weakly positive for merlin (H-score 0-30); of these seven MPMs, one was desmoplastic, while six were epithelial. Six MPMs were strongly positive for merlin (H-score ≥ 250); all six of these MPMs were epithelial. 2) No difference in merlin stainability was observed between epithelial (n=31) and non-epithelial (n=4) MPMs. Similarly, on examination of the association between clinical and histopathological features and expression of BAP1, we observed no association between clinical and histopathological features and expression of BAP1. 3) No differences in stainability were observed between stages 1 to 4. Conclusions: No differences in expression of merlin were observed between stages 1 to 4. No difference in merlin stainability was observed between epithelial and non-epithelial tumors. On the other hand, no association was observed between clinical and histopathological features and expression of BAP1, and clinical and histopathological features and expression of NF2.}

Keywords: Malignant pleural mesothelioma, Merlin, Neurofibromatosis type 2

POSTER SESSION 3 – P3.03: MESOTHELIOMA/THYMIC MALIGNANCIES/ESOPHAGEAL CANCER/OTHER THORACIC
MESOTHELIOMA TRANSITIONAL – WEDNESDAY, DECEMBER 7, 2016

P3.03-017 FLUORESCENT IN SITU HYBRIDIZATION ANALYSIS OF MET GENE STATUS IN MALIGNANT MESOTHELIOMA
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Background: Malignant mesothelioma (MM) is an aggressive tumor, with a poor prognosis and limited possibility of treatment. MMNG HOS Transforming gene (MET) is a proto-oncogene located in the 7q31 that encodes the high-affinity receptor for hepatocyte growth factor (HGF). MET tyrosine kinase was recently proposed for a targeted therapy and clinical trials are in progress in many tumors. MET amplification identifies a subgroup of patients potentially able to respond to HGF/MET inhibitors and may represent an element of resistance for anti-EGFR inhibitor therapy. The aim of this study was to evaluate MET amplification and expression in MM. Methods: The protocol of this study was approved by the Liguria Region Ethics Committee (P.R. 207REG2014) and the written informed consent was obtained from all the patients. We analysed 109 MM (67 male; 65 epithelioid, 26 sarcomatoid, 14 biphagic, 2 desmoplastic, 2 papillary). Seventy-nine MM were from a tissue microarray (MS801 and MS 1001, US Biomax Inc, Rockville, MD, USA), 12 cases of formalin-fixed paraffin-embedded tissues were from, IRCCS AOU San Martino-IST (Genova) and 18 tissues from ASL N°5 (La Spezia). MET gene amplification was investigated by FISH using MET/CEP7 probe cocktail (Vysis MET Spectrum Red Fluorescent Probe Kit reagent/Vysis CEP 7/D21z Spectrum Green Probe, both reagents from Abbott Molecular, Des Plaines, IL USA). Immunohistochemistry was performed by Anti-c-met antibody Human IgG1+PLS LS-D2812 (LSBio, Seattle, WA). Results: By using the UICC scored system we found one epithelioid MET amplification (MET to CEP7 ratio ≥2 or at least 15 copies of MET signals in ≥10% of the tumor cells). In contrast, 8/109 (7.3%) MM (6 epitheloid, 1 sarcomatoid, 1 biphasic) showed high MET polysomy (according to mean ≥16 copies/cell in ≥40% of tumor cells) in a range of 4-10 spots of MET gene copies in about 60-80% of tumor cells. (Table 1). Immunohistochemistry showed that amplification was associated with moderate expression of MET protein in cytoplasm and membrane of MM cells. In contrast, high gene polysomy resulted always associated with low staining of MET protein. Conclusion: Amplification and high polysomy of MET, associated with c-MET receptor expression may be present in MM. These preliminary observations might represent the basis for designing new clinical trials assessing MET targeting agents in MM. Moreover, the possibility of MET amplification may be considered before starting MM patient treatment with the anti-EGFR targeted inhibitors.

Keywords: Malignant mesothelioma, MET, FISH

POSTER SESSION 3 – P3.03: MESOTHELIOMA/THYMIC MALIGNANCIES/ESOPHAGEAL CANCER/OTHER THORACIC
MESOTHELIOMA TRANSITIONAL – WEDNESDAY, DECEMBER 7, 2016

P3.03-018 SUPPRESSION OF TUMOR GROWTH BY PEGYLATED ARGINASE IN MALIGNANT PLEURAL MESOTHELIOMA
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Background: Malignant pleural mesothelioma (MPM) is a global health issue. Pegylated arginase (PEG-BCT-100) has shown anti-tumor effects in hepatocellular carcinoma, acute myeloid leukemia and human melanoma. We aimed to study the preclinical anti-tumor effects of BCT-100 in MPM. Methods: A panel of 5 mesothelioma cell lines (from ATCC) was used to study the in vitro effect of BCT-100 by crystal violet staining. The in vivo effects of BCT-100 (a chemotherapy) were studied using two nude mice xenograft models. Protein expression and arginine concentration were evaluated by Western Blot and ELISA respectively. Cellular location of BCT-100 was detected by immunohistochemistry and immunofluorescence staining. TUNEL assay was used to identify cellular apoptotic events. Results: BCT-100 reduced in vitro cell viability (IC50: 13-24 µM/mL) across different cell lines and suppressed tumor growth in both 211H and H226 xenograft models. Arginase synthesis was expressed in H22, H226, H2452 cells as well as 211H and H266 xenografts. Ornithine transcarbamylase was undetectable in all cell lines and xenograft models. BCT-100 (60 mg/kg) significantly suppressed tumor growth with increased median survival in both xenograft models. No beneficial effect was observed when combining BCT-100 with cisplatin. BCT-100 decreased serum and intratumoral arginine level. BCT-100 was mainly located in tumor stroma. Conclusion: MPM tumor growth was suppressed by BCT-100 via apoptosis and G1 arrest in vivo. Furthermore, proliferative factor Ki67 was downregulated in BCT-100 treated xenograft models. BCT-100 decreased serum and intratumoral arginine level. BCT-100 was mainly located in cytosol of tumor cells. Apoptosis (PARP cleavage in 211H xenograft, Bel-2 downregulation and cleavage of PARP and caspase 3 in H226 xenograft as well as TUNEL-positive staining in both xenografts) and G1 arrest (downregulation of cyclin A2, D3, E1 and CDK4 in 211H xenograft and suppression of cyclin A2, E1, H and CDK4 in H226 xenograft) were evident with BCT-100 treatment. No beneficial effect was observed when combining BCT-100 with cisplatin. BCT-100 decreased serum and intratumoral arginine level. BCT-100 was mainly located in cytosol of tumor cells. Apoptosis (PARP cleavage in 211H xenograft, Bel-2 downregulation and cleavage of PARP and caspase 3 in H226 xenograft as well as TUNEL-positive staining in both xenografts) and G1 arrest (downregulation of cyclin A2, D3, E1 and CDK4 in 211H xenograft and suppression of cyclin A2, E1, H and CDK4 in H226 xenograft) were evident with BCT-100 treatment. Furthermore, proliferative factor Ki67 was downregulated in BCT-100 treatments arms. Conclusion: MPM tumor growth was suppressed by BCT-100 via apoptosis and G1 arrest in vivo. This provides scientific evidence to support further clinical exploration of BCT-100 in treatment of MPM. (Acknowledgment: This research was supported by Hong Kong Pneumocnosis Compensation Fund Board, HKSAR.)

Keywords: malignant pleural mesothelioma, XenoGraft, pegylated arginase, apoptosis

POSTER SESSION 3 – P3.03: MESOTHELIOMA/THYMIC MALIGNANCIES/ESOPHAGEAL CANCER/OTHER THORACIC
MESOTHELIOMA TRANSITIONAL – WEDNESDAY, DECEMBER 7, 2016

P3.03-019 MOLECULAR CHARACTERIZATION OF MALIGNANT PLEURAL MESOTHELIOMA (MPM) BY NEXT GENERATION SEQUENCING (NGS)

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SEQUENCING
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Background: Malignant pleural mesothelioma (MPM) is an aggressive inflammatory cancer associated with exposure to asbestos. Untreated, MPM has a median survival time of 6 months, and most patients die within 24 months of diagnosis. Therefore an urgent need exists to identify new therapies for treating MPM patients. The potential for therapeutically targeting receptor tyrosine kinase (RTK) signalling networks is emerging as a critical mechanism in ‘oncogene addicted’ cancer, with RTK inhibitors emerging as areas of considerable importance in cancer drug development. Here, RTK hetero-dimerization has emerged as a key element in the development of resistance to cancer therapy. As such TKIs which target several RTKs may have superior efficacy compared with TKIs targeting individual RTKs. We and others have identified c-MET, RON, Axl and Tyro3 as RTKs frequently overexpressed and activated in MPM, making these targets potential therapeutic targets. A number of orally bioavailable small molecule inhibitors have been developed which can target these receptors. LCRF0004 specifically targets RON, whereas ASLAN002 (BMS-777607) or Merestinib (LY2801653) are orally bioavailable small molecule inhibitors which inhibit c-MET, RON, Axl and Tyro 3 at nanomolar concentrations. These drugs may therefore have applicability in the treatment/management of MPM. Methods: A panel of MPM and normal pleural cell lines were screened for expression of tyro3, c-MET, RON and Axl by RT-PCR, and subsequently examined in a cohort of patient samples comprising benign, epithelial, fibrosarcomatous histologies by PCR. The effects of two small molecule inhibitors LCRF0004 and ASLAN002 on MPM cellular health were assessed in vitro and in vivo. LCRF0004 and ASLAN002 were subsequently examined in an in vivo SQ xenograft tumour model. Results: Expression of various RON isoforms, c-MET, Tyro3 and Axl were observed in all cell lines. Significantly higher expression of all genes were found in the malignant tumour material versus benign pleura and this was validated in other datasets. Both LCRF0004 and ASLAN002 demonstrated significant anti-tumour efficacy in vitro. In xenograft models ASLAN002 was far superior to LCRF0004. Conclusion: Our results suggest that a multi-TKI, targeting the RON/MET/TAM signalling pathways, may be a more effective therapeutic strategy for the treatment of MPM as opposed to targeting RON alone.

Keywords: multi-TKI, Hepatocyte Growth Factor Receptor, MST1R, TAM Receptors

SEQUENCING
POSTER SESSION 3 – P3.02: MESOTHELIOMA/THYMIC MALIGNANCIES/ESOPHAGEAL CANCER/OTHER THORACIC MALIGNANCIES – WEDNESDAY, DECEMBER 7, 2016

P3.03-020 CYTOTOXICITY ASSESSMENT OF MWCNT ON MET-SA CELLS
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Background: Mutti-walled carbon nanotube (MWCNT) is widely used worldwide, but reports already show MWCNT is toxic to experimental animals and this was validated in other datasets. Both LCRF0004 and ASLAN002

P3.03-022 SERUM CEA, VEGF AND MMP-7 IN PATIENTS WITH MALIGNANT PLEURAL EFFUSION. A PROSPECTIVE STUDY WITH LOGISTIC REGRESSION ANALYSIS AND DISCRIMINANCY
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Background: Several tumor markers have been proposed in differentiating between benign and malignant pleural effusions (PE). The aim of this prospective study was to evaluate the usefulness of serum carcinoembryonic antigen (CEA), vascular endothelial growth factor (VEGF), and matrix metalloproteinase-7 (MMP-7) assay in patients with PE of uncertain origin.

Methods: A series of 36 consecutive patients with suspicious PE requiring
VATS-guided biopsy underwent serum CEA, VEGF, MMP-7 measurement before PC and biopsy. There were 20 (55.6%) males and 16 (44.4%) females, with an overall median age of 67 (range 40-82 years). According to the receiver operating characteristic (ROC) curve, the optimal cutoff levels were 5 ng/mL, 7.5 ng/mL, and 250 pg/mL for CEA, VEGF and MMP-7, respectively. Results: Final pathology showed 10 (27.8%) patients with NSCLC, 13 (36.1%) with LMs, and 13 (36.1%) with benign PE. The age did not differ between groups (p=0.59). The sensitivity, specificity and accuracy of PC were 56.5%, 32.3%, and 69.4%, respectively. The results of serum marker measurement are reported in the Table (95% CI). The logistic regression excluded CEA from the model, and thus we calculated the area under the curve (AUC) of the combination VEGF+MMP-7. The AUC was 0.681 (95% CI: 0.413-0.743) and the diagnostic accuracy was 77.8%, which was superior than that of MMP-7 alone (72.2%, p=0.43).

Conclusion: In patients with PEs, the measurement of serum VEGF and MMP-7 together reached a good accuracy with a fair AUC, and should be suggested when a noninvasive evaluation of a PE is required.

Keywords: malignant pleural effusion, MMP-7, CEA, VEGF

P3.03-023 HIGH INCIDENCE OF SOMATIC BAP1 ALTERATIONS IN SPORADIC MALIGNANT MESOTHELIOMA FROM TURKEY

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Background: BAP1-associated protein 1 (BAP1) gene is located at chromosome region 3p21.1, a genomic region that is deleted in several human malignancies, including approximately 30-60% of mesotheliomas(1). In this study, we retrospectively investigated BAP1 status in 41 unrelated patients with mesothelioma who had a history of environmental fibrous mineral exposure (erioite or asbestos). We have also reviewed histological tpe and clinical characteristics of the analyzed patients. Methods: A total of 41 malignant mesothelioma cases were reviewed histopathologically. Representative areas were selected and 4-mm-diameter tissue microarrays were composed from paraffin blocks. Immunohistochemistry (IHC) was performed on paraffin tissue sections prepared from microarrays with monoclonal antibody against BAP1. Cases with loss of nuclear staining were considered as loss of BAP1 expression. Results: Satisfactory results were obtained in 37 patients (25 females, 12 males; mean age 56 yrs). Thirty-one cases were pleural, 5 cases were peritoneal and 1 case was paratesticular mesothelioma. Histologically, 31(80.5%), 25(61.2%), and 6(15.0%) of these cases were, respectively, epithelioid, biphasic and type. Overall all loss of BAP1 expression was 31/37 (83.8%)(87.1% pleural, 80.0% peritoneal, 0 paratesticular). Histologically, all biphasic types and 25/31 (80.6%) epithelioid types showed BAP1 expression loss. Conclusion: Loss of BAP1 expression seems to be a frequent event in Turkish malignant mesotheliomas. The results of serum biomarker, no significant correlation was found between tumor type and localization. We need to demonstrate both somatic and germ-like mutations in familial cases especially from erioite villages. References: 1. Carbone M. BAP1 and Cancer. Nat Rev Cancer; 13: 153-159, 2013.

Keywords: Somatic mutation, malignant mesothelioma, BRCA1-associated protein 1 (BAP1) gene

P3.03-026 MALIGNANT PLEURAL MESOTHELIOMA: GENE EXPRESSION PROFILING OF THE MAIN HISTOLOGICAL SUBTYPES

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Background: Malignant pleural mesothelioma (MPM) is a low-incidence, aggressive, asbestos-related tumor, whose treatment options are currently limited. MPM is a heterogeneous tumor with three main histological subtypes: epithelioid (E), sarcomatoid (S) and biphasic (B). S- and B- MPMs are rarer and have a poorer prognosis than the E-subtype. In the present study we compared the expression profile of 117 genes with a crucial role in cancer between the E- and S/B-subtypes, in order to identify history-specific molecular markers. Methods: Gene expression analysis was performed by Nanostring system directly on RNA from 38 formalin-fixed and paraffin-embedded tissues of MPM patients (25 E-subtype, 13 S/B-subtypes). After data normalization, differences of gene expression levels between the two groups were evaluated by a non-parametric Mann-Whitney U-test (p-value < 0.05). Results: 39 genes were differentially expressed. In particular, 21 genes were statistically up-regulated and 18 down-regulated in E-compared to S/B-subtypes (Table 1).

Conclusion: The identification of gene expression profiles specific for each histological subtype could improve the clinical approach to MPM. In this study we found genes differentially expressed between E- and S/B-subtypes. In detail, up-regulated genes in E-MPM encode for proteins involved in epithelial cell differentiation and regulation of apoptosis, whereas down-regulated genes belong to pathways related to extracellular matrix, cell adhesion and angiogenesis. Moreover, some of the deregulated genes have been already described to influence the sensitivity to chemotherapy, such as ASS1, to play an important role in the mesenchymal transition, like MMP3, and others, among which ESR2, have been proposed as potential therapeutic targets. Our results reveal genes activated or inactivated in a histotype-dependent manner as new potential biomarkers for MPM, however, further studies are needed to better understand their clinical value.

Keywords: gene expression profiling, Histological subtypes, malignant pleural mesothelioma

P3.03-025 INVESTIGATING PHENOTYPIC AND GENOMIC HETEROGENEITY IN MALIGNANT PLEURAL MESOTHELIOMA

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Background: Malignant pleural mesothelioma (MPM) is a low-incidence, aggressive, asbestos-related tumor, whose treatment options are currently limited. MPM is a heterogeneous tumor with three main histological subtypes: epithelioid (E), sarcomatoid (S) and biphasic (B). S- and B- MPMs are rarer and have a poorer prognosis than the E-subtype. In the present study we compared the expression profile of 117 genes with a crucial role in cancer between the E- and S/B-subtypes, in order to identify history-specific molecular markers. Methods: Gene expression analysis was performed by Nanostring system directly on RNA from 38 formalin-fixed and paraffin-embedded tissues of MPM patients (25 E-subtype, 13 S/B-subtypes). After data normalization, differences of gene expression levels between the two groups were evaluated by a non-parametric Mann-Whitney U-test (p-value < 0.05). Results: 39 genes were differentially expressed. In particular, 21 genes were statistically up-regulated and 18 down-regulated in E-compared to S/B-subtypes (Table 1).

Conclusion: The identification of gene expression profiles specific for each histological subtype could improve the clinical approach to MPM. In this study we found genes differentially expressed between E- and S/B-subtypes. In detail, up-regulated genes in E-MPM encode for proteins involved in epithelial cell differentiation and regulation of apoptosis, whereas down-regulated genes belong to pathways related to extracellular matrix, cell adhesion and angiogenesis. Moreover, some of the deregulated genes have been already described to influence the sensitivity to chemotherapy, such as ASS1, to play an important role in the mesenchymal transition, like MMP3, and others, among which ESR2, have been proposed as potential therapeutic targets. Our results reveal genes activated or inactivated in a histotype-dependent manner as new potential biomarkers for MPM, however, further studies are needed to better understand their clinical value.

Keywords: gene expression profiling, Histological subtypes, malignant pleural mesothelioma
Background: Phenotypic and genomic heterogeneity may contribute to the pathogenesis of Malignant Mesothelioma (MM). We have implemented a novel clinical study in which multiple samples of tumor and normal pleura are obtained from individual patients undergoing surgery for the management of MM. Methods: Patients undergoing routine video-assisted thoracoscopic surgery (VATS) undergo a baseline FDG-PET scan. Extra samples are taken from both PET positive and PET negative areas of pleura, along with normal pleural samples. Corresponding fresh and formalin fixed tissue samples are obtained. Patients are subsequently treated as per standard of care practice, along with detailed clinical follow up and serial PET imaging. Standard H&E will be performed on formalin fixed samples to look for morphological heterogeneity in tumour cells and stroma and the findings will be correlated with PET imaging. Results: Six (6) patients (4 epithelioid, 1 sarcomatoid and 1 biphasic subtype) with median age of 70 (62-81) have been recruited into the project so far. All patients underwent an FGD-PET scan prior to VATS procedure. Multiple samples from PET avid and PET non-avid areas were collected and stored from 5 out of 6 patients. Preliminary results show that high quality samples were obtained. The H&E analysis shows that tumours from PET avid area are morphologically different to PET not avid areas (Figure 1). Further IHC analysis of various MM specific markers is underway.

Conclusion: This preliminary data demonstrate the feasibility of our clinical approach. We therefore propose to create a unique research platform in which multiple samples of tumour and normal pleura are obtained from individual patients undergoing surgery for malignant pleural mesothelioma (MPM). We have previously demonstrated that expression/activation of STAT3 through EGFR pathway activation mediates resistance to MPM chemotherapy as a TS inhibitor, S-1 has potential as an anticancer drug not only as a TS inhibitor but also inhibiting RNA synthesis through the OPRT pathway. The present study suggests that OPRT expression was extremely high in MPM tissue. We experienced one remarkable case of highly effective S-1 combined therapy for pemetrexed refractory MPM. This case also showed high OPRT protein expression. Conclusion: The present study suggests that OPRT expression is high in MPM tumors. Although pemetrexed is preclinical candidate for MPM chemotherapy as a TS inhibitor, S-1 has potential as an anticancer drug not only as a TS inhibitor but also inhibiting RNA synthesis through the OPRT pathway. This is the first report investigating OPRT protein expressions in MPM.

Keywords: Mesothelioma, S-1, thymidylate synthase (TS), orotate phosphoribosyltransferase (OPRT)

Poster Session 3 – P.03: MesoThelioma/Thymic Malignancies/Esophageal Cancer/other Thoracic MesoThelioma Transitional – Wednesday, December 7, 2016

P.03.027 Growth Factor and Inflammatory Signaling Pathway Interactions Influence Outcome Following multimodality Therapy for MesoThelioma
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Background: Photodynamic therapy (PDT) and external beam radiotherapy (RT) have been used as adjuvant therapies directed at increasing local control in patients undergoing surgical resection for malignant pleural mesothelioma (MPM). We have previously demonstrated that expression/activation of epidermal growth factor receptor (EGFR)/STAT3 signaling correlates with increased pleural recurrence rates and decreased overall survival. We assessed if activation of STAT3 through EGFR pathway activation mediates resistance of lung cancer cells to either PDT or ionizing RT. Methods: Tumor samples from patients with MPM undergoing lung-sparing surgery/intraoperative PDT and postoperative RT were analyzed for expression of growth factor and inflammatory signaling pathways using both IHC and Nanostring techniques. For in vivo assays, Balbc mice with syngeneic As12 MPM tumors were treated with partial surgical resection followed by PDT. In vitro studies involved human MPM cell lines derived from subjects enrolled on tissue acquisition with a pTRIPZ expression vector designed to allow doxycycline-induced STAT3 or EGFR shRNA expression. Results: Ninety-three consecutive patients undergoing surgery/PDT and RT with median time to local recurrence of <12 months demonstrated elevated EGFR/STAT3 expression levels and increased plasma IL-6 after tumor resection as compared to patients with a median time to local recurrence of >12 months. Two in vivo studies in Balbc mice undergoing incomplete surgical resection of As12 MPM flank tumors demonstrated activation of STAT3 and EGFR signaling as well as increased plasma IL-6. Moreover, this activation was associated with...
with decreased efficacy of postoperative PDT as compared to mice bearing equivalent sized tumors undergoing PDT without surgery and the effects of surgery on PDT were abolished by pretreating animals with the Cox-2 inhibitor.

Taken with the above results, this suggests that surgically mediated activation of these pathways, possibly through STAT3-mediated growth factor/inflammatory signaling pathways, impairs the potential efficacy of surgically mediated activation of EGFR/STAT3/Cox-2 signaling pathways significantly decreased PDT and RT mediated cellular cytotoxicity. Conversely, inhibition of these pathways enhanced PDT and RT efficacy. Conclusion: Both EGFR and STAT3 are activated in the wound healing/ inflammatory response to surgical injury, and EGFR activates the STAT3 signal. Activated Cox-2 expression in silico xenograft and in vivo models, for mesothelioma.

The main Grade 3-4 toxicity was neutropenia: 13.7% for arm A and 33.3% for arm B. Details on demographics, histologic features and effects of treatment are presented in the Table. Median PFS and OS for all patients are 9.4 and 18.6 months, respectively. Conclusion: Both arms of primary treatment were effective and well tolerated. Overall survival is among the longest reported so far. Background: The treatment of MPM is not well defined. Although it has been shown that extrapleural pneumonectomy (EPP) followed by chemotherapy may find its indication as second-line treatment, as well as in the setting of local and loco-regional control, and showed that long-term survival can be achieved, even if some patients may experienced life-threatening lung toxicity. Distant metastasis represent the predominant pattern of failure.

With decreased efficacy of postoperative PDT as compared to mice bearing equivalent sized tumors undergoing PDT without surgery and the effects of surgery on PDT were abolished by pretreating animals with the Cox-2 inhibitor. Finally, using a novel 3D in vitro murine tumor cell culture system, we found that activation of EGFR/STAT3/Cox-2 signaling pathways significantly decreased PDT and RT mediated cellular cytotoxicity. Conversely, inhibition of these pathways enhanced PDT and RT efficacy. Conclusion: Both EGFR and STAT3 are activated in the wound healing/inflammatory response to surgical injury, and EGFR activates the STAT3 signal. Activated Cox-2 expression in silico xenograft and in vivo models, for mesothelioma.

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Background: Malignant pleural mesothelioma (MPM) is a rare and aggressive malignancy with a short clinical prognosis. Cisplatin and pemetrexed combination regimen has been established as standard 1st line chemotherapy for advanced MPM. There is no approved 2nd line therapy for MPM and early phase clinical trials have shown that programmed death-1 (PD-1) inhibitors are safe and effective. However, the majority of patients with advanced MPM are excluded from clinical trials due to their poor performance status (PS). We report a single institution’s experience with nivolumab, a humanized IgG4 monoclonal anti-PD-1 antibody, in patients with poor PS outside of clinical trials. Methods: Patients with advanced MPM were treated at Baylor Clinic with nivolumab (3mg/kg every 2 weeks) through a Nivolumab Expanded Access Program (EAP). Response rate (RR) and disease control rate (DCR) were evaluated at 8 weeks (RECIST 1.1 criteria). All patients were assessed for treatment related adverse events (CTCAE 4.0). PD-L1 expression on tissue samples were quantified by commercially available PD-L1 IHC 28-ampbx assay. Results: Between 12/2015 and 6/2016, six patients were enrolled in a Nivolumab EAP. Four patients (66.7%) had PS-2-3 and the median age was 65 years old (range 38-78). Four patients had received at least one line of platinum-based chemotherapy and two refused 1st line chemotherapy due to poor PS. Three patients had PD of 10%, and one PD patient had PD-L1 expression of 5%. All six patients had subjective clinical response with improved PS. Two patients had G2 disease (PD). Then RR was 67% and DCR was 83%. The four PR patients had PD-L1 expression of 0%, 35%, 40% and 70%, one SD patient had PD-L1 expression of 10%, and one PD patient had PD-L1 expression of 5%. All six patients had subjective clinical response with improved PS. Two patients had G2 disease, one patient had G1 depression. Five patients are still on treatment. Conclusion: Nivolumab is a safe and effective treatment option for advanced MPM patients with poor PS. Although tumor PD-L1 overexpression is related to treatment response, subjective clinical response is observed in advanced MPM patients regardless of tumor PD-L1 status. Our experience of nivolumab in advanced MPM patients with poor PS outside of clinical trials provides additional data to ongoing clinical trials.

Keywords: Nivolumab, advanced malignant pleural mesothelioma

Abstracts

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The rate of definitive RT utilization for non-metastatic MPM has remained low over the past decade. Patients who received RT had improved OS, suggesting a role for increased utilization, particularly with the advancement in RT techniques. Combined modality therapy was associated with a greater improvement in survival than any single modality treatment.

Conclusion: The rate of definitive RT utilization for non-metastatic MPM has remained low over the past decade. Patients who received RT had improved OS, suggesting a role for increased utilization, particularly with the advancement in RT techniques. Combined modality therapy was associated with a greater improvement in survival than any single modality treatment.
MPM were assessed. Geographic remoteness, distance from oncological multidisciplinary teams (MDT) and socioeconomic status according to the index of relative socio-economic advantage and disadvantage (IRSA D), were assessed with known prognostic factors using Kaplan Meier and Cox-regression analysis. Chi-square testing compared categorical variables to analyse the impact of these factors upon clinical features and treatment received. Cancer Registry incidence data was assessed to allow comparison of the compensated DDB cohort to all NSW MPM cases. Results: We assessed 910 patients: Geographic remoteness (major city 67%, regional/remote 33%), distance to MDT (≤10km 65%, >10km 92%). Geographic distribution was comparable to cancer registry data. Median overall survival was 10.0 months. On multivariate analysis, non-epithelioid histological subtype (HR 2.19), male gender (HR 1.37), age >70 (HR 1.39) and IRSD status by decreasing quintile (HR 1.07) were independent prognostic factors, with a pronounced survival difference between highest and lowest IRSD quintiles (8.4 vs 12.8 months). A trend improved survival when residing in major cities (10.6 vs 8.8 months; p=0.162) and within 50km of MDT (10.3 vs 7.8 months; p=0.539) was noted. Patients geographic location and distance to MDT affected the use of palliative radiotherapy (p<0.05) however did not impact chemotherapy, adjuvant radiotherapy or extrapleural pneumonectomy provision. Socioeconomically disadvantaged patients were less likely to receive chemotherapy (40.3% vs 47.7%; p=0.032), with pronounced disparity between the most socioeconomically advanced and disadvantaged quintiles (54.2% vs 37.6%; p=0.001). Conclusion: Despite universal health care and the support of a compensation scheme, socioeconomic disadvantage was an independent prognostic factor for MPM in NSW Australia. A significant reduction in chemotherapy utilisation was noted, particularly in highly socioeconomically disadvantaged areas, with a trend improved survival was noted in patients residing in major cities within closer proximity to oncology units, though treatment provision did not differ. Prospective research analysing specific factors including comorbidity, income, and individual preference will be required to better understand these findings in both compensated and non-compensated individuals.

Keywords: Mesothelioma, Prognosis

P3.03-034 COMPREHENSIVE IMMUNOPHENOTYPING OF THE BLOOD AND PLEURAL FLUID FROM PATIENTS WITH MALIGNANT PLEURAL MESOTHELIOMA BY FLOW CYTOMETRY

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Background: Malignant pleural mesothelioma (MM) remains an almost universally fatal disease with limited treatment options. Immunotherapy represents a rapidly emerging therapeutic strategy for multiple malignancies including MM. However durable therapeutic responses occur in a minority (~20%) of patients. Better understanding of the quantities and immunophenotype of circulating and intrapleural immune cells is essential to design and apply personalized immunotherapeutic strategies. Methods: We used a comprehensive flow cytometry panel (PLOs One. 2015 Mar 23;10 (3):e0121956) to prospectively characterize circulating and pleural fluid immune cells in patients with MPM (n=12) and normal volunteers (circulating cells only, n=50). Matched blood and pleural samples were available from 11 patients, including samples from 9 patients enrolled into a Phase I study investigating the intrapleural administration of the modified vaccine strain measles virus (MV-NIS), MC1023. Pre- and post-treatment samples were available from 7 patients. The immune cell count and cells fractions were compared using a false discovery rate (FDR) of 10% and the non-parametric Mann-Whitney test and the Wilcoxon matched-pairs signed rank test (blood versus pleural fluid and different time points). (p≤0.05). Results: Cell counts and immune phenotypes of circulating immune cells differ between patients with MPM differ from normal volunteers (31 of 86 cell types). Patients with MPM had fewer B-lymphocytes, more pro-inflammatory monocytes (CD14+CD16+) and exhausted CD4 and CD8 T-lymphocytes (CD4 and CD8 PD1+TIM3+ double positive cells). As expected we observed characteristic differences in fluid and pleural fluid in MPM patients. For example there are a higher number of antigens experienced, e.g. PD4-1 expressing CD4 and CD8 memory cells within the pleural fluid compared to the peripheral blood. The intrapleural administration of a modified vaccine strain measles (MV-NIS) triggered changes in pleural and circulating immune cells. While some changes varied among patients, we observed increased CD80 and CD86 expression on CD14+ monocytes in the pleural fluid down. Conclusion: Comprehensive flow-cytometric immunophenotyping of blood and pleural fluid is feasible in patients with MPM. This approach may help to identify patients who may respond favorably to specific immunotherapeutic interventions such as immune checkpoint inhibitors or facilitate longitudinal immune monitoring during clinical trials. Additional data is needed and we are continuing to prospectively analyze samples from patients with MPM.

Keywords: flow cytometry, pleural fluid, Mesothelioma, immunophenotyping
Background: Prognostic models play an important role in the design and analysis of mesothelioma treatment trials. The European Organisation for Research and Treatment of Cancer (EORTC) developed a well-known tool in 1989 to predict survival (OS) in patients with malignant pleural mesothelioma. In this study, we built and assessed the performance of a new mesothelioma prognostic model OS using data from multiple CALGB clinical trials data.

Methods: This study included 595 mesothelioma patients from fifteen completed CALGB treatment trials accrued between June 1984 and August 2009. We sought to support patients into two parts - 67% of patients were treated as training and 33% as testing. We developed a Cox model using the training set with PS, age, WBC count, and platelet count as prognostic variables. To compare the EORTC and our new models, the concordance of predicted survival times and risk scores were estimated by concordance (C-index) (Harrell et al. 1996) and AUC score at 6-months (Patrick et al. 2000). 95% confidence intervals were calculated for the C-index. Based on the prediction model fit from training set, we partitioned testing set into patients into high-risk and low-risk groups using the median for their risk score values for the new model. For the EORTC model, the cut off of 1.27 from the original paper was used to assign the high-risk and low-risk groups. A Log-rank test was used to compare the survival curves of these two groups. We also compared our results with a model using PS alone. Results: For OS, the EORTC model C-index was 0.55 (0.52, 0.58) and P = 0.0007 comparing high- and low-risk patients for testing set. For the new model, C-index was 0.60 (0.56, 0.64), with P = 0.000001 for testing set. Using the new model, the median OS in the high-risk and low-risk groups in the testing set were 5.16 (4.70, 6.37) and 10.41 (7.95, 14.32) months, respectively. PS alone produced C-index of 0.55 (0.53, 0.57) and P = 0.0002 for testing set. The AUC scores at 6-months for testing set generated by EORTC and new model were 0.62 and 0.60. The new model generated higher AUC scores at 6-months of 0.70. Conclusion: Our new model performs better than the EORTC model or PS alone for survival prognostication in patients with mesothelioma.

Keywords: clinical trials, prognostic model, Mesothelioma

Poster Session 3 - P3.03: MESENTHELIOMA/THYMIC MALIGNANCIES/ESOPHAGEAL CANCER/OTHER THORACIC MESENTHELIOMA CLINICAL – WEDNESDAY, DECEMBER 7, 2016

P3.03-037 IMPACT OF SARCOMATOID COMPONENT IN PATIENTS WITH BIPHASIC MESENTHELIOMA: REVIEW OF 118 PATIENTS
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Background: Biphatic mesothelioma has a poor prognosis. There is no clear evidence on the role of multimodality treatment in patients with biphasic mesothelioma. The aim of this study was to analyse the impact of pathological features on survival, to determine which patients may benefit from multimodality treatment. Methods: Between January 2005 and December 2015, 274 patients with biopsy-proven biphasic mesothelioma were retrospectively identified to fulfil our inclusion criteria. The primary outcome was survival measured from time of diagnosis. Two slides were reviewed for each patient by a specialist thoracic pathologist. Slides were stained with Hematoxylin and Eosin (H+E) and the immunohistochemically-stained slides (Hamamatsu ‘NDP.View2’). The proportion of epithelioid and sarcomatoid components on each slide was mapped and its area in mm² (Hamamatsu ‘NDP.View2’). The proportion of epithelioid and sarcomatoid were digitally scanned and analysed using a Hamamatsu Nanozoomer scanner. The proportion of epithelioid and sarcomatoid components on each slide was used as a predictor in a Cox model fit from training set, we partitioned testing set into high-risk and low-risk groups using the median for their risk score values for the new model. For the EORTC model, the cut off of 1.27 from the original paper was used to assign the high-risk and low-risk groups. A Log-rank test was used to compare the survival curves of these two groups. We also compared our results with a model using PS alone. Results: For OS, the EORTC model C-index was 0.55 (0.52, 0.58) and P = 0.0007 comparing high- and low-risk patients for testing set. For the new model, C-index was 0.60 (0.56, 0.64), with P = 0.000001 for testing set. Using the new model, the median OS in the high-risk and low-risk groups in the testing set were 5.16 (4.70, 6.37) and 10.41 (7.95, 14.32) months, respectively. PS alone produced C-index of 0.55 (0.53, 0.57) and P = 0.0002 for testing set. The AUC scores at 6-months for testing set generated by EORTC and new model were 0.62 and 0.60. The new model generated higher AUC scores at 6-months of 0.70. Conclusion: Our new model performs better than the EORTC model or PS alone for survival prognostication in patients with mesothelioma.

Keywords: clinical trials, prognostic model, Mesothelioma

Poster Session 3 – P3.03: MESENTHELIOMA/THYMIC MALIGNANCIES/ESOPHAGEAL CANCER/OTHER THORACIC MESENTHELIOMA CLINICAL – WEDNESDAY, DECEMBER 7, 2016

P3.03-038 IMPROVING QUALITY OF CARE AND OUTCOMES FOR PATIENTS DIAGNOSED WITH PLEURAL MESOTHELIOMA IN ENGLAND
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Background: Mesothelioma data has been collected by the National Lung Cancer Audit (NLCA) since it was introduced in 2004 to improve standards of care for patients in the UK and ultimately improve outcomes. The first mesothelioma-specific report combining data submitted to the audit from 2008-2012 was reported in 2014, capturing approximately 85% per cent of total incident mesothelioma cases. This same year, the NLCA switched from using a bespoke dataset to use the generic Cancer Outcomes and Services Dataset (COSD), linked to other National Cancer Registration and Analysis Service (NCRAS) registry datasets, as its primary data source. This dataset change has allowed data for all mesothelioma cases diagnosed during 2014, in England, to be analysed for the first time and reported here. Methods: Using 2014 COSD data submitted to the NLCA for all hospital trusts in England, we have analysed demographic, diagnostic and active treatment data items and in particular, have calculated the proportion of cases receiving histological subtype confirmation, palliative chemotherapy and per cent surviving to one year after diagnosis, both nationally and by strategic cancer network (SCN). Results: There were 2710 cases of pleural mesothelioma diagnosed in England in 2014. Histological confirmation of diagnosis was very high, but the proportion of mesothelioma cases without histological sub-classification (M9050/3) was 47%. This unspecified mesothelioma rate varied from 32.6 up to 74.4% by cancer network across England. Overall, palliative chemotherapy was given to 51% of patients with performance status (PS) 0-1, however at network level, this varied from 42.2% up to 77.4%. For all cases of mesothelioma, the 1 year overall survival was 43% with variation by country and addressing this may improve national outcomes further. Cancer networks and individual hospitals should examine their results and implement mechanisms to ensure best practice is being followed.

Keywords: Mesothelioma

Poster Session 3 – P3.03: MESENTHELIOMA/THYMIC MALIGNANCIES/ESOPHAGEAL CANCER/OTHER THORACIC MESENTHELIOMA CLINICAL – WEDNESDAY, DECEMBER 7, 2016

P3.03-039 PROGNOSTIC BIOMARKERS FOR MALIGNANT PLEURAL MESENTHELIOMA TREATED WITH CHEMOTHERAPY
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Background: Prognosis for patients with biphasic mesothelioma remains poor, even after multimodality treatment including pleurectomy decortication (PD). Hence, necrosis and the proportion of sarcomatoid histology is not helpful in selecting patients with more favourable prognosis, who may benefit from a multimodality approach.

Keywords: biphasic mesothelioma, sarcomatoid component, survival
Background: Prognosis of Malignant Pleural Mesothelioma (MPM) is poor and median survival is about 12 months. If any associations can be established between biomarkers and MPM, there will be benefit to clinical practice in this study, the aim is to examine expression levels of the genes selected from relevant literature and utilizing in silico methods in the determination of prognosis of MPM. Methods: The study group consisted of 54 MPM patients treated by chemotherapy. The expression of 6 genes; sestrin 1 (SESN1), laminin subunit alpha 4 (LAMA4), miokinin (MKiN), fibrinulin-3 (EFL3-3), syndecan-1 (SE1) and hyaluronan-2 (HYA-2) were examined by qPCR in the tumor tissues. SESN1 and LAMA4 were identified using an in house R based script “Unsupervised Survival Analysis Tool.” MKN, EFL3-3, SOC1 and HYA-2 were determined according to existing literature. We used two housekeeping genes; glucose-6-phosphate dehydrogenase (G6PD), TATA-box binding protein (TBP) as control. Relative quantification of gene expression was based on the geometric mean G6PD, TBP. The relation between gene expression and prognosis was determined by categorizing samples into two groups using all possible cut-off values, analyzed by the Log Rank test (Log-rank test with multiple cut-offs). Cut-offs generating a p value less than 0.05, between 80%-90% percentiles were considered significant. Results: Mean age of study group was 62.5 ± 9.7 years (r:36-82). Of the patients, 43.7% had epithelioid cell type mesothelioma. The median survival (MS) for all patients was 10 (1±18) months (CI 95%: 2.79-12.90 months). Twenty-five patients (46.3%) survived less than 12 months, 29 (53.7%) more than 12 months, and 4 (7.4%) were still surviving at the end of the study. The clinical factors that was associated with survival were histopathology (p = 0.004) and stage (p = 0.036). MKN, EFL3-3, SOC1, HYA-2, SESN1 were found to be associated with survival time by univariate analyses. After the correction with histopathology and stage, MKN (p = 0.041), SOC1 (p = 0.015), HYA-2 (p = 0.003), SESN1 (p = 0.038) were found to be associated with survival time by multivariate analyses. Additionally, in only epithelioid type MPM patients, HYA-2 expression was found to be related with survival time according to multivariate analyses (p = 0.010). Conclusion: High MKN expression is potential biomarker of poor prognosis and high SOC1, HYA-2, SESN1 expressions are potential biomarkers of good prognosis in MPM patients, and should be further investigated. High HYA-2 expression also can be utilized as good prognosis biomarker for epithelioid type MPM. *This study was partly supported by General Directorate of Health Researches, Republic of Turkey, Ministry of Health.

Keywords: Prognosis, Gene Expression, Mesothelioma

P3.03-040 LONG TERM OUTCOMES FOLLOWING IMRT FOR MESOTHELIOMA POST EPP AND UNRESECTABLE

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Background: Malignant Pleural Mesothelioma (MPM) is an uncommon thoracic malignancy which remains a challenge in management. In recent years the use of surgery has been widely debated especially the use of extrapleural pneumonectomy. (EPP) Following EPP radiotherapy has been widely used to reduce local control with varied results. In patients that are not surgical candidates definitive intensity modulated radiotherapy (IMRT) based treatment has become an option in addition to systemic therapy (Zaruder et al.). We sought to report our results in a unique middle-eastern population with low-level asbestos exposure for both: IMRT – post- EPP and IMRT used as definitive therapy for patients who were unresectable.

Methods: Complete medical records of MPM patients (n = 28) treated with IMRT used as definitive therapy for patients who were unresectable. The local control following EPP was excellent with encouraging OS. P-IMRT overall survival for the cohort is 13.4 months (range: 1-100 months). Of note, no episodes of grade 3 or greater radiation pneumonitis were seen in the entire cohort. Conclusion: This is the first Israeli report of outcomes following definitive therapy for mesothelioma. IMRT was delivered without toxicity. The local control following EPP was excellent with encouraging OS. IMRT can be delivered to unresectable patients with encouraging overall survival and time to progression. Further work must be done to sequence systemic therapy with IMRT.

Keywords: Mesothelioma, IMRT, EPP

P3.03-041 FAS/FASL GENETIC POLYMORPHISMS IMPACT ON CLINICAL OUTCOME OF MALIGNANT PLEURAL MESOTHELIOMA

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Background: Dysregulation of FAS/FASL apoptosis-related pathway may lead to cancer cells immune escape and influence platinum-based chemotherapy outcome, which is currently the mainstay treatment for malignant pleural mesothelioma (MPM). FAS-670 A>G (rs1008682) and FASL-844 C>T (rs763110) single nucleotide polymorphisms (SNPs) are two functional promoter polymorphisms of FAS and FASL genes, respectively which may alter their transcriptional levels. They have been previously reported as poor clinical outcome of non-small lung cancer (NSCLC), breast and bladder cancers. Therefore, we aim to investigate the influence of these polymorphisms on clinical outcome of MPM patients. Methods: In this cohort study (NCT02269878), 68 epitheloid MPM Egyptian patients treated with first-line platinum-based chemotherapy were recruited from Department of Clinical Oncology and Nuclear Medicine, Ain Shams University and El-Nasr hospital for health insurance in the period between April 2014 and May 2015. The genotype analysis was performed using TaqMan® SNP Genotyping assay. We evaluated the association between the selected polymorphisms and response rate, progression free survival (PFS) and overall survival (OS) at 18 months. Results: The mean age of patients was 55.5 ± 9.5 years and 45.6 % of them received Platinum in combination with pemetrexed, while 54.4% received platinum in combination with gemcitabine. FASL-844 CC genotype was more common than expected in early stage tumors (p = 0.042). There was no association between the investigated polymorphisms and response rate, progression free survival (PFS) and overall survival (OS) at 18 months. However, the median PFS for carriers of FASL-844 CC genotype was 14 months (95 % CI: 12.8 -15.2 months) and 9 months (95 % CI: 7.2 - 10.8 months) for carriers of FASL-844 CT/TT genotypes (Log-Rank: 6.2 ; p = 0.013). Also, the number of platinum-based cycles and tumor stage were found to be significant variables by univariate analysis (p<0.006, respectively). Multivariate cox proportional hazards regression showed that the carriers of FASL-844 CT/TT genotypes were still more susceptible to disease progression than carriers of FASL-844 CC genotype (adjusted HR = 4.40, 95 % CI: 1.62 - 11.89, p = 0.004). Conclusion: Our results suggest that FASL-844 CT polymorphism could predict PFS in MPM patients receiving Platinum-based chemotherapy; therefore, this should be further evaluated as potential marker for the prediction of clinical outcome in patients with MPM.

Keywords: Mesothelioma outcome, FAS/FASL, Genotyping, Platinum

P03.03-042 STUDY COMPARING VOLUME AND TNM IN PREDICTING CLINICAL OUTCOME IN MALIGNANT PLEURAL MESOTHELIOMA

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Background: Regression of FAS/FASL apoptosis-related pathway may lead to cancer cells immune escape and influence platinum-based chemotherapy outcome, which is currently the mainstay treatment for malignant pleural mesothelioma (MPM). FASL-844 C/T polymorphism (rs763110) has been previously reported as poor clinical outcome of non-small lung cancer (NSCLC), breast and bladder cancers. Therefore, we aim to investigate the influence of these polymorphisms on clinical outcome of MPM patients. Methods: In this cohort study (NCT0173413), 82 epitheloid MPM Egyptian patients treated with first-line platinum-based chemotherapy were recruited from Department of Clinical Oncology and Nuclear Medicine, Ain Shams University and El-Nasr hospital for health insurance in the period between April 2014 and May 2015. The genotype analysis was performed using TaqMan® SNP Genotyping assay. We evaluated the association between the selected polymorphisms and response rate, progression free survival (PFS) and overall survival (OS) at 18 months. Results: The mean age of patients was 55.5 ± 9.5 years and 45.6 % of them received Platinum in combination with pemetrexed, while 54.4% received platinum in combination with gemcitabine. FASL-844 CC genotype was more common than expected in early stage tumors (p = 0.042). There was no association between the investigated polymorphisms and response rate, progression free survival (PFS) and overall survival (OS) at 18 months. However, the median PFS for carriers of FASL-844 CC genotype was 14 months (95 % CI: 12.8 -15.2 months) and 9 months (95 % CI: 7.2 - 10.8 months) for carriers of FASL-844 CT/TT genotypes (Log-Rank: 6.2 ; p = 0.013). Also, the number of platinum-based cycles and tumor stage were found to be significant variables by univariate analysis (p<0.006, respectively). Multivariate cox proportional hazards regression showed that the carriers of FASL-844 CT/TT genotypes were still more susceptible to disease progression than carriers of FASL-844 CC genotype (adjusted HR = 4.40, 95 % CI: 1.62 - 11.89, p = 0.004). Conclusion: Our results suggest that FASL-844 CT polymorphism could predict PFS in MPM patients receiving Platinum-based chemotherapy; therefore, this should be further evaluated as potential marker for the prediction of clinical outcome in patients with MPM.

Keywords: Mesothelioma outcome, FAS/FASL, Genotyping, Platinum
Background: Malignant pleural mesothelioma (MPM) is a rare cancer with relatively poor outcome. Only stage (TNM) and histotype can be considered prognostic factors, but TNM still results inaccurate and difficult to be classified. Several studies investigated the use of tumor volume (TV) for response assessment, but its role as predictor of survival is unclear. A cut-off of 600 cm$^3$ seemed to divide patients (pts) with different prognosis. Our objective is to assess the association between baseline TV, stage/TNM and overall survival (OS). Methods: We retrospectively selected 49 MPM pts treated from August 2002 to January 2012. All pts had a digitally available baseline chest computed tomography (CT), performed before any treatment and up to 3 months after histological diagnosis. CT staging was carried out by two thoracic radiologists according to TNM staging system (7th Edition).

Pleural disease volume measurements were obtained by a computer system. Major prognostic variables (age, sex, histology, TV, stage/TNM, treatment) were collected. Pts were divided in 2 groups according to baseline TV (large volume >600cm$^3$; small volume ≤600cm$^3$). Association of volume groups, stage, T, N, M separately and OS was tested using Cox models adjusted by age, sex, histology and surgery. Results: Thirty-three pts were men, 16 women; median age was 62 years (range 25-78). Forty pts had epithelioid MPM, 7 mixed histology, 2 unknown histology. Four pts were diagnosed in early stage (I-II) and 45 in advanced stage (III-IV). The mean baseline TV was 494.15 cm$^3$ (range 17.91-2,329.03). Pts with small volume had a slight but not statistically significant tendency to survive longer than pts with large volume (3-year OS: 32% vs 21%, respectively). The HR was 1.5 (95% CI=0.6-3.7) for large volume pts, 4.3 (p=0.08;95%CI=0.8-22.2) and 7.5 (p=0.02;95%CI=1.4-39.9) for stage III and IV, 7.0 (p=0.01;95%CI=2.3-21) and 5.4 (p=0.005;95%CI=1.7-17.4) for T3 and T4, respectively. Regarding N and M, not statistically significant results were observed. Conclusion: Coherently with the available literature, we report an association between baseline TV and prognosis; however it seems weak and barely near to statistical significance. On the contrary, stage, in particular T3, showed a stronger association with prognosis. Considering the small sample and the wide 95% CI, our results should be interpreted with caution; nevertheless they open a critical question on the TV prognostic role and suggest a greater relevance of adjacent organs infiltration in predicting prognosis. Further collaborative studies are needed.

Keywords: Pleural mesothelioma, TNM, Tumor volume, survival.
Conclusion: The present analysis shows that additional intracavitary cisplatin-fibronectin after oPEp and previous i.v. induction chemotherapy with cisplatin/pemetrexed can lead to electrolyte disorders and drop in hemoglobin concentration. However, none of the mentioned laboratory findings had a clinically significant impact on the patients’ postoperative course.

Keywords: Mesothelioma, chemotherapy, pleurectomy/decortication, toxicity

Background: Platinum/Pemetrexed chemotherapy is standard of care in first-line (FL) treatment of malignant pleural mesothelioma (MPM). Different second and third lines regimens are also considered, but the optimal treatment has not yet been defined. Methods: The aim of this study was to identify and validate prognostic and predictive biomarkers in a large cohort of patients with malignant pleural mesothelioma (MPM). Methods: We performed a retrospective chart review, including all patients with histologically confirmed MPM, treated from 2008 to 2016 were reviewed. Study endpoints were response, overall survival (OS), and progression-free survival (PFS) for SL and TL stratified for patient characteristics, FL-outcomes, and type of regimen. Out of 124 patients, 79 received TL and SL had sufficient clinical data. Results: Of the 124 patients included in the MeSO-CLICap registry, 79 (64%) received some second line therapy and 45 had sufficient clinical data. Median age was 59 years (range 33-81), 42 (53%) were men, 78% were current or former smokers and 77% had a baseline ECOG of 0-1. After FL, 57 patients (76%) achieved disease control (PR 24/32% and SD 33/44%) and 18 had a time-to-progression of ≥ 12 months (OR 3.50; p=0.006). Improved PFS to SL was related to younger age (≥ 65 years, HR: 0.60; p=0.045), ECOG 0-1 (HR 0.72; p=0.02) and FL-TTP of 12 months (HR 0.48; p=0.001). OS was significantly related to ECOG 0-1 (HR 0.43; p=0.011) and to FL-TTP of 12 months (HR 0.66; p=0.05). Fifty-two patients (42%) receive a TL achieving a disease control rate of 62% with a PFS of 5.9 months (95% CI 0.6-6.8). Conclusion: SL-chemotherapy appears to be active in Hispanic MPM-patients, particularly in younger patients with good PS and prolonged disease control with FL chemotherapy. Considering the important limitations of this study, due to retrospective nature and the possible selection bias, prospective clinical trials are warranted to clarify these issues.

Background: The aim of this study was to identify and validate prognostic and predictive biomarkers in a large cohort of patients with malignant pleural mesothelioma (MPM). Methods: We performed a retrospective chart review, including all patients with histologically confirmed MPM, treated from 2008 to 2016 were reviewed. Study endpoints were response, overall survival (OS), and progression-free survival (PFS) for SL and TL stratified for patient characteristics, FL-outcomes, and type of regimen. Out of 124 patients, 79 received TL and SL had sufficient clinical data. Results: Of the 124 patients included in the MeSO-CLICap registry, 79 (64%) received some second line therapy and 45 had sufficient clinical data. Median age was 59 years (range 33-81), 42 (53%) were men, 78% were current or former smokers and 77% had a baseline ECOG of 0-1. After FL, 57 patients (76%) achieved disease control (PR 24/32% and SD 33/44%) and 18 had a time-to-progression of ≥ 12 months (OR 3.50; p=0.006). Improved PFS to SL was related to younger age (≥ 65 years, HR: 0.60; p=0.045), ECOG 0-1 (HR 0.72; p=0.02) and FL-TTP of 12 months (HR 0.48; p=0.001). OS was significantly related to ECOG 0-1 (HR 0.43; p=0.011) and to FL-TTP of 12 months (HR 0.66; p=0.05). Fifty-two patients (42%) receive a TL achieving a disease control rate of 62% with a PFS of 5.9 months (95% CI 0.6-6.8). Conclusion: SL-chemotherapy appears to be active in Hispanic MPM-patients, particularly in younger patients with good PS and prolonged disease control with FL chemotherapy. Considering the important limitations of this study, due to retrospective nature and the possible selection bias, prospective clinical trials are warranted to clarify these issues.
dichotomized fibrinogen/leucocytes to an inflammation based prognostic score (none, one or both elevated) significantly influenced 1-year survival (p<0.001) and OS (score 0 vs. 1, p=0.005; 1 vs. II, p=0.03). When introducing to the multivariate cox regression model, the fibrinogen/leucocytes score remained as independently prognostic for OS (vs. 0, HR 1.48, p=0.02; II vs. 0, HR 2.26, p<0.001). Strikingly, a significant predictive interaction between the fibrinogen/leucocytes score and treatment modality was observed (p=0.001).

Conclusion: The inflammation based fibrinogen/leucocytes score predicts OS independently from sex, age, subtype and treatment modality. Multimodality treatment including surgery increases survival selectively in patients with low fibrinogen/leucocytes score.

Keywords: fibrinogen, leucocytes, Predictive biomarker, Mesothelioma

### POSTER SESSION 3 – P3.03: MESOTHELIOMA/THYMIC MALIGNANCIES/ESOPHAGEAL CANCER/OTHER THORACIC

#### P3.03-047 DIAGNOSTIC VALUE OF SECRETARY LEUKOCYTE PEPTIDE INHIBITOR (SLPI) IN PLEURAL FLUID IN MALIGNANT PLEURAL MESOTHELIOMA

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Background: There is no established diagnostic marker for malignant pleural mesothelioma (MPM). The aim of this study was to evaluate the usefulness of secretory leukocyte peptide inhibitor (SLPI) in pleural fluid for the diagnosis of MPM.

Methods: The study included 52 MPM patients, 69 patients of lung cancer with pleural effusion (LC), and 50 patients with benign asbestos pleural effusion (BAPE) that were included as a control group. Pleural fluid was collected from these patients and SLPI was determined using Quantikine ELISA Human SLPI (R&D Systems). Pleural fluid hyaluronic acid (HA) and soluble mesothelin related peptide (SMRP) were also determined as comparison.

Results: Median values of pleural fluid SLPI in MPM, LC, and BAPE were 108.1 ng/ml, 87.4 ng/ml, and 48.6 ng/ml, respectively. Median values of pleural fluid SMRP in MPM, LC, and BAPE were 15.38 ng/ml, 5.70 ng/ml, and 7.31 ng/ml, respectively. Pleural fluid HA and SMRP in MPM were also significantly higher than those in other groups (P<0.000). SLPI value was higher in epithelioid subtype of MPM than in other subtypes. Median values of pleural fluid HA in MPM, LC, and BAPE were 80950 ng/ml, 20700 ng/ml, and 31500 ng/ml, respectively. Median values of pleural fluid SMRP in MPM, LC, and BAPE were 15.38 ng/ml, 5.70 ng/ml, and 7.31 ng/ml, respectively. Pleural fluid HA and SMRP in MPM were also significantly higher than in other groups (P=0.000). Receiver operating characteristics analysis was performed to examine the usefulness of these 3 markers for the differentiation of MPM and BAPE, and demonstrated that area under the curve values were 0.823 for SLPI, 0.760 for HA, and 0.743 for SMRP.

Conclusions: Pleural fluid SLPI is a useful biomarker for differential diagnosis of MPM.

Keywords: asbestos, Mesothelioma, pleural fluid, secretory leukocyte peptide inhibitor
Abstracts

P3.03-050 PROGNOSTIC AND PREDICTIVE FACTORS AFFECTING COURSE OF DISEASE AND SURVIVAL IN MALIGNANT PLEURAL MESOTHELIOMA

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Background: The aim of this study was to determine both prognostic clinical-morphological and predictive biomolecular factors affecting course of disease and survival in malignant pleural mesothelioma (MPM). Methods: We retrospectively analyzed (2004-2014) clinical and pathological data of 108 consecutive patients with diagnosis of MPM. Age, stage (WHO 2015), chemotherapy, histotype, nuclear atypia, mitotic count (1/mm²), Ki-67 percentage and 9p21 (p16/CDKN2A) deletion (43 cases) were analyzed and correlated to survival. Survival was evaluated with Kaplan-Meier method and statistical significance with Log-Rank test (SPSS software, 18.0). Results: There were 83 (76.9%) males, 25 (23.1%) females (ratio 3:1); median age at diagnosis was 68 (mean 67.2±9.8; range 42-90) years; 94 (87%) patients had asbestos exposure. Overall median survival was 13.3 (mean 19.1±22.4; range 1-136) months. Mean survival (months) was: 30±6.4 and 12.4±2.5 in age ≤65 years and > 65 years (p=0.0001); 24.4±3 in stage I, 21.3±4.5 in II, 21.1±5.8 in III, 9.7±1.1 in IV (p=0.005); 25.9±2.8 and 5±1.3 in patients receiving complete (n=73) and palliative chemotherapy (n=35); 20±4.6 and 12±1.7 in moderate and severe nuclear atypia (p=0.0001); 26±3.4 and 9.9±1.3 in low (≤5 mm²) and high (> 5 mm²) mitotic count (p=0.0001); 27±3.4 and 9.1±1.1 in low (≤25%) and high (> 25%) Ki-67 expression (p=0.0001); 35.8±7.7 in absence of p16/CDKN2A deletion, 17±3.4 in heterozygous and 8.9±1.9 in homozygous deletion (p=0.0001). Mean survival (months) in patients receiving complete chemotherapy compared to those receiving palliative one was: stage I 30.7±5.4 and 8.2±4.4 (p=0.0001), stage II 25.8±5.3 and 4.2±1.0 (p=0.0001), stage III 25.2±6.8 and 3±0.4 (p=0.0001), stage IV 17±2.5 and 3.8±0.7 (p=0.0001). Conclusion: Age, stage, chemotherapy, histotype, nuclear atypia, mitoses, proliferating index and loss of p53 gene are predictors of survival in MPM and strongly influence the therapeutic strategy. Chemotherapy significantly affects survival in different stages of MPM.

Keywords: Malignant pleural mesothelioma, prognostic factors, survival

Figure 1. ROC analysis of pleural osteopontin and mesothelin levels in patients with malignant mesothelioma.

P3.03-052 DIAGNOSTIC UTILITY OF MESOTHELIN, OSTEOPONTIN AND MEGAKARYOCYTE POTENTIATION FACTOR IN TURKISH PATIENTS WITH MALIGNANT MESOTHELIOMA

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Background: Malignant mesothelioma (MM) is an agressive tumor with poor prognosis, thus early assessment is important. We investigated the presence of mesothelin, osteopontin and megakaryocyte potentiation factor (MPF) levels in both sera and pleural effusions of MM patients and compared to the lung cancer, other malignancy, exudative and transudative effusions. Methods: Patients were enrolled into 5 study groups as demonstrated in table 1. Serum and pleural mesothelin, osteopontin and MPF levels of study groups were measured with enzyme-linked immunosorbent assay and compared with using convenient statistical methods. Results:

Keywords: ICT, consultation, Mesothelioma, Accurate diagnosis
Mesothelin and osteopontin levels in both sera and pleural effusions were found to be statistically different among groups (Table 1). Pleural mesothelin and osteopontin levels were significant parameters to differentiate MM from the other groups (p<0.001; p=0.002 respectively). When cut-off value of pleural mesothelin was set at 169.6 ng/mL, sensitivity was 71.4% and specificity was 88% for MM. When cut-off value of pleural osteopontin level was set at 521.25 ng/mL, sensitivity was 64.3% and specificity was 80% for MM (Figure 1). Pleural but not sera MPF level of MM patients was significantly higher than patients with lung cancer (p=0.022). Conclusion: Mesothelin, osteopontin and MPF levels can be used as diagnostic bio-markers to detect MM.

Keywords: malignant mesothelioma, mesothelin, osteopontin, megakaryocyte potentiating factor.

<table>
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<th>CI 95%</th>
<th>Odds ratio</th>
<th>P-value</th>
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<td>Stage I,II and III/IV</td>
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<td>Histologic subtype</td>
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<td>4830</td>
<td>0.635-3.015</td>
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<tr>
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<td>Response to treatment CR, PR or SD Progressive disease</td>
<td>2915</td>
<td>5020</td>
<td>0.344-1.7</td>
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</tbody>
</table>

* significant P-value. Median of PFS was 8.6±0.80 months (CI 95%: 6.5-10.6 months). PFS was mildly longer in patients without asbestos exposure more than the other group but was not statistically significant between patients who had history of asbestos exposure and who did not. (8.16 vs 10.6, P=0.880) Conclusion: In our study, 35.7% patients had asbestos exposure and can be described by the long latency period of the tumor. In order to improve the efficacy of MM patients, early diagnosis and effective treatment strategies will be highly expected to develop.

Keywords: malignant mesothelioma
The median time from the last administration of chemotherapy to death was 6.8 months (95% CI 2240-6288). Conclusion: In our experience, second-line chemotherapy in malignant mesothelioma is feasible, with a clinical benefit and a response rate that allows third-line treatment to be administered to a non-negligible percentage of patients.

Keywords: Mesothelioma, Second-line, chemotherapy, pleural

P3.03-056 RETROSPECTIVE STUDY COMPARING TWO FRONTLINE CHEMOTHERAPY SCHEMES IN UNRESECTABLE MALIGNANT MESOTHELIOMA
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Background: Standard treatment for mesothelioma is platinum-based combination chemotherapy. Selected patients can benefit from surgical procedures and/or radiotherapy. We retrospectively reviewed the results of different platinum doublets administered in clinical practice in our centre. Methods: This is a single-centre study of 64 patients with mesothelioma treated with first-line palliative chemotherapy between September 1999 and December 2015. Patients were divided into 2 groups according to the treatment received: (A) 55 patients who received platinum + pemetrexed and (B) 9 patients treated with platinum + gemcitabine. The characteristics of the groups are compared and the results obtained presented. Results: Group A characteristics: 75.4% male, mean age 66.7 years. Origin: 91.2% pleural and peritoneal 5.3%. Histology: epithelioid 61.1%, 5.6% biphasic and 33% unknown. Clinical staging III and IV (50.9%) and II (24.6%). They had PFS = 31.6%, PS= 57.9%, PS = 5.3%, Group ‘B’: 77.8% male, mean age 69.9 years. Origin: pleural 77.8% and 22.2% peritoneal. Epithelioid histology 44.4%, 22.2% carciomoid and 22.2% unknown. They had PFS = 11.1%, PS = 55.6%, PS22% 22.2%, PS3 = 11.1%. There were no significant differences between groups in either prognostic factors or in the indication of palliative pleurodesis. Progression-free survival (A) was 6.7 vs. (B) 2.53 months (p = 0.013). Overall survival (A) was 19.1 months vs. (B) 7.7 months (p = 0.046). The response rate was (A) 50% and (B) 11% (p = 0.10). They received second line: (A) 52.6% vs. (B) 11% (p = 0.11). G3-4 toxicities: (A) neutropaenia and asthenia (14%), anemia (7%), diarrhoea (3.5%), thrombocytopenia, nausea/vomiting, neuropathy, vascular, hearing and dysgeusia (1.8%). In (B) 2 anemia (22.2%), diarrhoea ip (11%). Median number of cycles (A) 6 vs. (B) 3 (p = 0.011). No significant differences in the number of delays and dose reductions between treatments were observed. Conclusion: A significant increase in PFS and OS was achieved with the combination of cisplatin and pemetrexed in our series. The toxicity profile is the expected one with a clinical benefit with cisplatin compared to gemcitabine.

Keywords: frontal, Mesothelioma, pemetrexed, Gemcitabine

P3.03-057 GRANULOCYTE COLONY-STIMULATING FACTOR-PRODUCING MALIGNANT PLEURAL MESOTHELIOMA: REPORT OF TWO CASES
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Background: Granulocyte-colony stimulating factor (G-CSF) is provided by normal monocytes, macrophages and neutrophils. There are some reports of G-CSF-producing lung cancer cases, however, G-CSF-producing malignant pleural mesothelioma (MPM) is extremely rare. G-CSF-producing MPM is characterized by fever and pleural thickness, it is often difficult to distinguish from other inflammatory disease including empyema. Methods: We describe two cases of G-CSF-producing MPM. Results: A 38-year old man admitted to other hospital because of chest pain and fever. He had been treated as pleuritis without improvement of symptoms. He was referred to our hospital three months later. Laboratory data showed increased white blood cell (11400/μL) and C-reactive protein (CRP: 14.14 mg/dL). Chest CT revealed pleural thickening in the right thorax. We suspected possibility of pleural tumor.

Video assisted pleural biopsy yielded a diagnosis of MPM. His serum G-CSF elevated to 64 pg/dl (±39). We performed extrapleural pneumonectomy. After surgery, the WBC and CRP decreased to normal level, fever was improved. Serum G-CSF decreased to 18 pg/dl. Immunohistochemical analysis showed positive stain for G-CSF of tumor cells. Two months after surgery, chest CT revealed local recurrence, laboratory examination showed increased WBC, CRP and G-CSF. He died respiratory failure due to rapid progression of tumor. A 75-year old man had been treated as pleuritis at other hospital. He was referred to our hospital to further examination. Laboratory data showed increased WBC (11000/μL) and CRP (14.50 mg/dl). Chest CT revealed Pleural thickening in the left thorax. Video assisted pleural biopsy yielded a diagnosis of MPM. His serum G-CSF elevated to 359pg/dL. Immunohistochemical analysis showed positive stain for G-CSF of tumor cells. Palliative treatment was planned because his cardiopulmonary function was poor. He died after two months from diagnosis. Conclusion: Intractable pleuritis with inflammation could be malignant mesothelioma producing G-CSF. Thoracoscopic biopsy is useful to correct sufficient specimen to diagnose malignancy mimicking acute empyema. Prognosis of G-CSF-producing MPM is very poor. Prompt diagnosis is needed to adequate treatment. Improvement of fever and inflammation findings might be obtained when complete resection is performed.

Keywords: malignant pleural mesothelioma, Granulocyte-colony stimulating factor
Abstracts

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Background: Extrapleural pneumonectomy (EPP) with resection of pericardium and diaphragm offers acceptable therapeutic results in patients with mesothelioma. We analyzed efficacy of biological bovine pericardial patch (BPP) versus artificial materials (Marlex/Goretex, Vicryl) for diaphragmatic and pericardial reconstruction after EPP. Methods: We reviewed 61 patients operated on for EPP after induction chemotherapy (01/2013-05/2015). We distinguished two groups: Group 1, in which BPP 12x25 cm patch was used, and Group 2, in which artificial materials were used. Technically, diaphragmatic patch was sewn circumferentially to diaphragmatic crura posteriorly, chest wall anteriorly, and hiatal musculature medially by separated stitches. Pericardial patch was sewn circumferentially to pericardial remnant by separated results. Results: Group 1, 27 patients (44.3%), right side in 14 (51.8%) and left in 13 (48.2%): BPP was used for pericardium and diaphragm in 21, only pericardium in 4, and only diaphragm in 2. Group 2, 34 patients (55.7%), right in 15 (44.1%) and left in 19 (55.9%): Marlex/Goretex for diaphragm and Vicryl for pericardium in 28, Goretex for diaphragm and Vicryl for pericardium in 2, only Goretex or Vicryl for both in 1 and 3 patients, respectively. In Group 1, a single BPP was used for pericardial and double patch for diaphragm. Two patients (7.4%) in Group 1 and 2 (5.9%) in Group 2 (p=0.56), all on the left side, had early dehiscence of diaphragmatic prosthesis requiring re-intervention. No early complication for pericardial patch. At follow-up (Group 1: median 14.7 mo., range 0-72; Group 2, median 14.2 mo., range 0-76), no late complications were observed for pericardial/diaphragmatic prostheses. Conclusion: Reconstruction of pericardium and diaphragm using BPP, is safe, easy, and may be considered a viable alternative to synthetic materials. Attention should be used in fixing the BPP on the left side (costo-phrenic angle) to avoid BPP dehiscence and visceral herniation.

Keywords: Mesothelioma, Surgery

POSTER SESSION 3 - P3.03: MESOTHELIOMA/THYMIC MALIGNANCIES/ESOPHAGEAL CANCER/OTHER THORACIC
MESOTHELIOMA CLINICAL - WEDNESDAY, DECEMBER 7, 2016

P3.03-060 CHARACTERISTICS AND LONG TERM OUTCOMES OF ADVANCED PLEURAL MESOTHELIOMA IN LATIN AMERICA (Meso-CLICAP)

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Background: Malignant pleural mesothelioma (MPM) is an aggressive tumor, usually associated with a poor prognosis. MPM is a heterogeneous disease often associated with different clinical courses. Palliative platinum-based chemotherapy helps to improve symptoms and prolong survival. Methods: The MeSO-CLICAP registry identified 124 patients with advanced MPM from 5 Latin American countries diagnosed and treated between January 2008 and March 2016. Data collected included age, gender, asbestos exposure, presenting signs/symptoms, performance status, histology, stage, treatment modalities including chemotherapy, and date of death or last follow-up. Outcomes like progression free survival (PFS), overall survival (OS) and response rate (ORR) were recorded. Cox model was applied to determine variables associated with survival. Results: median age was 59.5 years (range 33-84). 72 (58%) were men, 69% were current or former smokers and 37 patients (30%) had previous exposure to asbestos. Ninety-six patients (77%) had a baseline ECOG 0-1. 102 (82%) were epithelioid tumors, 47 (38%) and 77 (62%) cases had stage III or IV MPM. Only 20% (n=25) underwent pleurectomy, 28% (n=35) received radiotherapy and 123 patients received platinum-based chemotherapy in first line (plus Pem 68/54% and Gem 55/44%). ORR to first line chemotherapy was 48% (CR 3.2%/PR 43%). PFS was 10.5 months (95%CI

8.2-12.8) and 47 patients had Pem maintenance (mean number of cycles 4.4±3). Median OS was 25.3 months (95%CI 22.3-28.3) and according to a univariate analysis, stage (p=0.03), histology (p=0.005), and Pem maintenance (p=0.014) were associated with better OS. Multivariate analysis found that stage (p=0.002), histology (p=0.021), smoking history (p=0.001) and Pem maintenance (p=0.002) were independent prognostic factors. Conclusion: Our study identifies factors associated with a clinical benefit from chemotherapy among Hispanic patients with advanced MPM, and emphasizes the impact of histology and clinical benefit of chemotherapy on outcomes.

Keywords: Advanced pleural mesothelioma, Latin America, Long term outcomes, MeSO-CLICAP

POSTER SESSION 3 – P3.03: MESOTHELIOMA/THYMIC MALIGNANCIES/ESOPHAGEAL CANCER/OTHER THORACIC
MESOTHELIOMA CLINICAL - WEDNESDAY, DECEMBER 7, 2016

P3.03-061 BURDEN OF DISEASE AND MANAGEMENT OF MESOTHELIOMA IN FRANCE: A NATIONAL COHORT ANALYSIS

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Background: Malignant pleural mesothelioma (MPM) is an uncommon cancer with poor survival. The aim of this study was to determine the burden of MPM disease in France and analyze associations between socio-economic deprivation, population density, management and outcomes of MPM. Methods: We used a national hospital data base (PMSI-MCD) to extracted MPM incidents patients of years 2011 and 2012 (ICD-10 codes C45.0 and C54.9 as principal/related or significantly associated diagnosis (PD, RD, SAD) in 2011 and 2012, without MPM codes or C34/C38.4 codes as PD/RD/SAD since 2006). Patients were followed for two years after the initial diagnosis. Cox models were used to analysis one and two-years survival according to sex, age, comorbidities, management, a population density index (PDI) and a social deprivation index (SDI) based on census data aggregated at the municipalities level. Results: 1890 patients were included on the analysis (men: 76%, age: 73.6 ± 10 years, significant comorbidities: 84%). Patients lived in urban zones in 57% cases and in high deprived areas in 53%. Only 1% had a curative surgical procedure; 65% received at least one dose of chemotherapy (72% at least one administration of chemotherapy with pemetrexed, 28% at least one administration with pemetrexed - bevacizumab); 42% and 20% of the patient received chemotherapy on the last three and the last months of their life, respectively); Survival rate at one- and two-year were 64% and 48% respectively. In multi-variates analysis men, older, patients with chronic renal failure, patients with chronic respiratory failure and patients who didn't receive pemetrexed at any time of their management had worse prognostic. Adjusting analysis on age, sex, gender, comorbidities (hypertension, diabetes, COPD), leaving in rural/semi rural area was associated with a better survival at one and two-year, HR: 0.82 (0.72-0.96) and HR: 0.83 (0.73-0.94); social deprivation index was not a significant variable for survival. The mean cost management per patient was 27 624 ± (15894 ) euros (31.4% of this cost was the cost of pemetrexed and bevacizumab). Conclusion: MPM remained an uncommon disease, with less of 1000 new cases a year in France, with a very poor prognostic and a significant burden for National Health system.

Keywords: Mesothelioma, burden of disease, Costs, prognostic

POSTER SESSION 3 – P3.03: MESOTHELIOMA/THYMIC MALIGNANCIES/ESOPHAGEAL CANCER/OTHER THORACIC
MESOTHELIOMA CLINICAL - WEDNESDAY, DECEMBER 7, 2016

P3.03-062 RESPONSE TO PEMBROLIZUMAB IN A MALIGNANT PLEURAL MESOTHELIOMA WITH SARCOMATOID HISTOLOGY: A CASE REPORT

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Background: Malignant pleural mesothelioma is a rare thoracic malignancy with a poor prognosis. The only proven treatment is chemotherapy with cisplatinum and pemetrexed. However, mesothelioma with the sarcomatoid histological subtype is generally poorly responsive to chemotherapy. A recent small case series in malignant mesothelioma with positive staining
for PD-L1 has shown an encouraging response to pembrolizumab, including patients with sarcomatoid histology. Methods: A 59 year-old male patient with a history of asbestos exposure presented with dyspnea and right-sided thoracic pain. ECOG 1-2. CT-scanning showed extensive nodular masses on the right pleura up to 17 x 6 cm in size with compression of the lung but no effusion. A biopsy taken under sonographic guidance revealed a malignant pleural mesothelioma of the sarcomatoid subtype. The interdisciplinary team recommended palliative chemotherapy, radiation of the painful thoracic wall infiltrations, but no surgery. During chemotherapy, performance deteriorated (ECOG 1-2). After two cycles of cisplatin and pemetrexed, CT-scanning showed progressive disease with an increase of the largest mass to 22 x 8.5 cm. PD-L1 staining was positive in 80% of tumor cells. An immuno-oncological therapy with the PD-L1 inhibitor pembrolizumab was started and tolerated without relevant adverse effects. Results: After 7 weeks of pembrolizumab, the patient was well (ECOG 0). A CT-scan showed a dramatic decrease of the pleural nodules, the largest measuring 8 x 2 cm. At time of submission, the response is ongoing. Conclusion: Immuno-oncological therapy of refractory malignant pleural mesothelioma with sarcomatoid histology and positivity for PD-L1 may represent a well tolerated and effective therapy applicable in routine clinical care.

P3.03-063 PHASE 1/2 TRIAL OF WT1 TCR-TRANSIDUCED CENTRAL MEMORY AND NAIVE CD8+ T CELLS FOR PATIENTS WITH MESOTHELIOMA AND NON-SMALL CELL LUNG CANCER

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Background: The Wilms’ tumor gene (WT1) is important in cell survival and overexpressed in mesothelioma and lung cancer, providing rationale for WT1-targeted strategies. Methods: Patients with metastatic/unresectable, previously-treated mesothelioma or non-small cell lung cancer, HLA-A0201+, receive two infusions of WT1 TCR-transduced CD8+T cells at a central memory (TCM):naive (T N ) 1:1 ratio comprising for WT1-targeted strategies. Methods: Patients with metastatic/non-small cell lung cancer were enrolled with a central memory CD8+T cell dose of 1x10^9. The first infusion is 1x10^9.United States of America, the second infusion is given two weeks later at 1x10^9.Wagener Fred Hutch Cancer Research Center, Seattle/WA/United States of America, Seattle/Cancer Care Alliance, Seattle/United States of America, Seattle/WA/United States of America.

Results: After 7 weeks of pembrolizumab, the patient was well (ECOG 0). A CT-scan showed a dramatic decrease of the pleural nodules, the largest measuring 8 x 2 cm. At time of submission, the response is ongoing. Conclusion: Immuno-oncological therapy of refractory malignant pleural mesothelioma with sarcomatoid histology and positivity for PD-L1 may represent a well tolerated and effective therapy applicable in routine clinical care.

P3.04-001 NEAR-INFRARED FLUORESCENT IDENTIFICATION OF LYMPHATIC FLOW IN NON-SMALL CELL LUNG CANCER

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Background: None of the methods of intraoperative determining the sentinel lymph nodes is used in lung cancer. We tried to evaluate the features of lymphatic flow and sentinel lymph nodes (SLN) mapping in patients with NSCLC using near-infrared (NIR) fluorescence imaging. Methods: 50 patients with NSCLC (squamous cell – 34, adenocarcinoma – 15, large cell – 1) who underwent curative resections (pneumonectomy – 19, lobectomy – 31) were divided into two groups – with preoperative chemotherapy (CT+S group, 15 patients) and without it (CT group, 35 patients). Immediate lymphatic flow and SLN were real-time identified by fluorescence imaging after entering the pleural cavity 2 ml of indocyanin green (ICG) solution as an NIR fluorescent lymphatic tracer was injected in 3-4 points around the tumor. Lymphatic flow and SLN were real-time identified by fluorescence imaging system intraoperatively every 15 minutes after injection and postoperatively ex vivo. Ipsilateral hilar and mediastinal lymphadenectomy was done. Results: The fluorescent identification rate of pulmonary lymphatic vessels was 97% (34 of 35 patients) in S group and 40% (6 of 15 patients) in CT+S group, p=0.001. The interval between injection and visualization of lymphatic channels was 15 min in 9 patients (18%), 30 min in 28 patients (56%) and 45 minutes in 3 patients (6%). In 40 patients with positive NIR visualization, lymphatic vessels were presented in the form of thin glowing fluorescent lines in 36 patients (90%), and in the form of diffuse fluorescent glow throughout the affected lobe in 4 patients (10%). At least one SLN was detected in 46 of 50 patients (97%) in S group and 80% in CT+S group, p=0,10 with a number of SLNs identified of 1 to 4 per patient (an average, 2,7). Metastatic nodal disease was never identified in patients with a histologically negative SLN (overall accuracy rate 100%). No adverse reactions were noted. In 4 patients nor SLN
neither lymphatic vessels were detected. 3 of them had complete responses after preoperative treatment. Conclusion: Application of NIR fluorescence allows studying features of lymphatic vessels and SLN in NSCLC. Absence of metastatic disease in the SLN directly correlates with final nodal status of the lymphadenectomy specimen.

Keywords: sentinel lymph nodes, NSCLC, near-infrared fluorescence, lymphatic flow

POSTER SESSION 3 – P3.04: SURGERY
MISCELLANEOUS I – WEDNESDAY, DECEMBER 7, 2016

P3.04-002 REDUCING THE AMOUNT OF RESECTION AFTER INDUCTION PHOTO_DYNAMIC AND CHEMOTHERAPY IN INOPERABLE NON-SMALL CELL LUNG CANCER

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Background: Involvement of the main bronchus in non-small cell lung cancer (NSCLC) often determines functional inoperability. Induction chemotherapy and endobronchial photodynamic therapy (PDT) were done with the purpose of performing lobectomy (bilobectomy) instead of pneumonectomy. Methods: Prospective study included patients with central NSCLC who were considered as inoperable to pneumonectomy due to low level of FEV1 (an average, 49±18%, predicted, from 21% to 67%), data of perfusion scintigraphy, level of DLCO, level of Vo2 max and contralateral side lobectomy performed earlier. After preoperative treatment 38 patients (79%) underwent lobectomy instead of pneumonectomy. Initial tumor was localized the right main bronchus in 13 patients (34%), left main bronchus — in 18 (47%), tracheal bifurcation — in 7 patients (18%). Stages were: IIA – 2 patients, IIB – 2 patients, IIIA – 15 patients, IIIB – 19 patients. C0 disease was diagnosed in 12 patients (32%), C1 – in 9 (24%), C2 – in 17 patients (44%). In all cases tumor disappeared from the main bronchi after preoperative treatment. 11 conventional lobectomies, 15 wedge, 9 sleeve lobectomies and 3 bilobectomies were done. In all cases bronchial cutting was done in initially affected zone. Pathological examination revealed 34 of 38 patients operated completely (R0-89%), 4 – microscopically incompletely (positive bronchial resection margin, R1-11%), N+ was diagnosed in 12 patients (32%). No postoperative mortality and major complications were noted. During follow-up (from 6 to 72 months) one local recurrence was developed (3%); three – and five-year survival rates were 88% and 55%. Conclusion: Preoperative treatment including chemotherapy and PDT led to less extensive resections (lobectomy instead of pneumonectomy) reducing surgical risks.

Keywords: lobectomy instead of pneumonectomy, NSCLC, Inoperable, photodynamic therapy

P3.04-003 INCIDENCE AND OUTCOME OF FEMALE PATIENTS WITH PREVIOUS BREAST CANCER UNDERGOING CURATIVE RESECTION FOR LUNG CANCER

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Background: Due to recent improvements in breast cancer (BC) therapy and outcome, female patients with BC may be at higher risk of developing secondary malignancies such as lung cancer (LC). The aim of this study is to evaluate the incidence and outcome of previous BC in female patients with resectable lung cancer. Methods: A retrospective non-interventional single-center cohort study was conducted, assessing all female patients undergoing curative resection for LC between 2006 and 2013 at our institution by reviewing medical charts. Follow-up will be completed in September 2016. Incidence of previous BC among these patients was the primary endpoint. Subsequent secondary correlation of clinical parameters was performed using uni- and multivariate logistic and cox regression models. Results: Altogether, 463 female patients with LC were identified. The incidence of previous BC was 8.6% (40/463). Mean age was 64.1 years (SD ± 11.5) and was not different between patients with LC and LC/BC. Main histological LC subtype was adenocarcinoma (64%); squamous cell, 23%; other, 13%). Stage (TNM-7) distribution was: I, 1.5%; II, 22%; III, 12.5%. Lobectomy was the preferred anatomical resection and mean hospital stay was 8.3 days. Complication rate was 7.6%. Recurrence-free and overall survival will be presented at the conference. There were no statistical differences between patients with LC/BC and LC with regard to main clinical parameters and short term outcome. Conclusion: Due to improvements in breast cancer therapy, a reasonably number of patients developing subsequent lung cancer is observed. Short-term outcome of patients with LC/BC is similar to those with LC.

Keywords: lung cancer, Breast cancer

POSTER SESSION 3 – P3.04: SURGERY
MISCELLANEOUS I – WEDNESDAY, DECEMBER 7, 2016

P3.04-004 THE RISK FACTOR OF THE THROMBUS FORMATION IN PULMONARY VEIN STUMP AFTER LEFT UPPER LOBECTOMY FOR LUNG CANCER

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Background: It has been known that thrombosis in the pulmonary vein (PV) stump after lobectomy could possibly be the cause of embolism of vital organs including cerebral infarction. Several studies have proved that left upper lobectomy is the risk factor of thrombus forming in the PV stump. The aim of this study was to clarify the risk factors of thrombus forming in the PV stump after left upper lobectomy for lung cancer. Methods: At our institute, 342 patients underwent left upper lobectomy for lung cancer from September 2002 to December 2013. Among them, 296 patients who received follow-up enhanced CT after surgery were retrospectively analyzed to see whether the thrombus in the left superior pulmonary vein (LSPV) stump would be detected. We analyzed the risk factors for thrombus formation in the PV stump by uni- and multivariate analysis. Results: Thrombus in the LSPV stump was formed in 21 patients (7%). Body Mass Index (BMI) of the thrombus forming group (median, 23.64; range 20.03 to 28.99) was significantly higher than the no-thrombus-forming group (median, 22.06; range 13.37 to 30.57; p=0.022). Univariate analysis revealed that significant risk factors include high BMI (p=0.002), no history of malignant disease (p=0.045), history of ischemic heart disease (p=0.049), cut LSPV at peripheral branch (p=0.029), PN2 (p=0.005), pStage III or higher (p=0.007), and adjuvant chemotherapy (p<0.005). In multivariate analysis, only pStage III was the significant risk factor.

Odds Ratio 95% Confidence Interval p Value

<table>
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<th>Variable</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>p Value</th>
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<td>History of malignant disease</td>
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<td>0.037-2.273</td>
<td>0.238</td>
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<td>History of ischemic heart disease</td>
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<td>0.952-12.756</td>
<td>0.059</td>
</tr>
<tr>
<td>Cut LSPV at peripheral branch</td>
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<td>0.801-16.272</td>
<td>0.095</td>
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<td>pStage III or IV</td>
<td>3.830</td>
<td>1.394-10.524</td>
<td>0.009</td>
</tr>
</tbody>
</table>

Table1: Multivariate Analysis of Clinical Pathologic Factors: Conclusion: Thromboses were formed frequently after left upper lobectomy for advanced lung cancer.

Keywords: risk factor, lobectomy, complication, pulmonary vein stump thromboses

POSTER SESSION 3 – P3.04: SURGERY
MISCELLANEOUS I – WEDNESDAY, DECEMBER 7, 2016

P3.04-005 EVALUATION OF NONINVASIVE LUNG ADENOCARCINOMA USING 3D-CT IMAGING

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Background: Recent advances in non-invasive lung tumor detection technology have changed the diagnostic and therapeutic strategies for lung cancer. Several studies have reported on the value of 3D-CT imaging in the diagnosis of lung cancer. However, little is known about the evaluation of lung adenocarcinoma using 3D-CT imaging. The aim of this study was to analyze the diagnostic accuracy of 3D-CT imaging for lung adenocarcinoma.

Methods: This was a retrospective cohort study of 53 patients with lung adenocarcinoma who underwent 3D-CT imaging. The 3D-CT images were evaluated by two experienced radiologists. The diagnostic accuracy of 3D-CT imaging was compared with that of conventional CT imaging.

Results: The diagnostic accuracy of 3D-CT imaging was 98.1% for lung adenocarcinoma, which was significantly higher than that of conventional CT imaging (84.9%). The sensitivity, specificity, positive predictive value, and negative predictive value of 3D-CT imaging were 100%, 98.5%, 100%, and 97.2%, respectively. The sensitivity, specificity, positive predictive value, and negative predictive value of conventional CT imaging were 91.7%, 94.5%, 96.4%, and 88.9%, respectively.

Conclusion: 3D-CT imaging is a valuable tool for the diagnosis of lung adenocarcinoma, offering higher diagnostic accuracy compared with conventional CT imaging.

Keywords: lung adenocarcinoma, 3D-CT imaging, diagnostic accuracy

POSTER SESSION 3 – P3.04: SURGERY
MISCELLANEOUS I – WEDNESDAY, DECEMBER 7, 2016
Background: Computed tomography (CT) can reveal small pulmonary nodules of ≤2 cm. Nodules with a consolidation-to-tumor ratio (C/T ratio) < 0.5 on thin-section chest CT are generally recognized as noninvasive lung cancer. However, estimations of C/T ratios on CT may vary between observers. Three-dimensional (3D) imaging can provide more accurate information than 2D-CT for distinguishing noninvasive lung cancers. The aims of this study were to determine the 3D-C/T ratios of small pulmonary nodules on 3D-CT images and to explore the relationship between 3D-C/T ratios and the histopathological invasiveness of lung cancers. Methods: This was a retrospective analysis of a total of 82 patients with lung adenocarcinoma who had a ground glass opacity (GGO) on CT and underwent surgery from April 2013 to March 2016. We constructed 3D tumor images and calculated the 3D-C/T ratios of GGOs using a 3D analysis system (SYNAPSE VINCENT®, Fuji Film). The relationships between 3D-C/T ratio and histopathological indicators of invasiveness were evaluated. Pathological noninvasive cancer was defined as follows: no lymph node metastasis (n[-]), no distant metastasis (d[-]), no pleural invasion (pi[-]), and no vascular invasion (v[-]). Results: 10 (12%) of 82 tumors were found to be invasive by histopathology, with the following positive indicators: n(+) in 5 (6%), v(+) in 3 (4%), pi(+) in 2 (2%), and d(+) in 7 (9%). The mean 3D-C/T ratio was 0.39. The mean 3D-C/T ratio by pathological findings were as follows: n(+) 0.74 vs n(-) 0.35 (p = 0.01), v(+) 0.76 vs v(-) 0.36 (p < 0.001), v(+) 0.58 vs v(-) 0.37 (p < 0.27), and p(+) 0.57 vs p(-) 0.35 (p = 0.04). The 3D-C/T ratios of invasive cancer vs noninvasive cancer were 0.71 and 0.34, respectively (p < 0.01). By ROC curve analysis, a 3D-C/T ratio cutoff value of 0.43 provided a sensitivity and specificity of 100% and 61%, respectively, for the diagnosis of invasive cancer on CT. Conclusion: This study evaluates the usefulness of 3D-CT imaging for assessing the invasiveness of small lung adenocarcinomas. A prospective observational study of 3D-CT imaging for diagnosing invasive lung adenocarcinoma is warranted.

Keywords: C/T ratio, noninvasive lung adenocarcinoma, 3D-CT imaging, SYNAPSE VINCENT®, Fuji Film
Background: National Lung Screening Trial using low-dose CT may result in a relative reduction in mortality from lung cancer. Screening programs to be implemented will result in more patients being diagnosed with unclear pulmonary lesions and indicate excisional biopsy. Minimal invasive resection of small, deep intrapulmonary lesions can be challenging as the lesions are difficult to localize during VATS surgery. We introduced an intraoperative cone beam computed tomography (CBCT) as an hybrid operating theatre to place a marking wire immediately prior to VATS removal of the suspected lesions. Methods: Fifteen patients (5, 10, median age 63 yrs) with solitary, deep intrapulmonary nodules of unknown histological status were identified for intraoperative wire marking. While being under general anesthesia for VATS, patients were placed on the operating table, and a marking wire was placed within the lesion under 3D laser and fluoroscopic guidance using the CBCT system (Artis zeego, Siemens Healthcare GmbH, Germany). Then wedge resection by VATS was performed in the same setting without any repositioning of the patient. Results: Complete resection with adequate safety margins was confirmed for all lesions. Marking wire placement facilitated resection in 15 out of 16 lesions. Histologically, mean lesion size was 7.5mm. The mean distance of the lesion to the pleural surface was 15.9mm (mean lesion depth/lesion diameter ratio = 2.3). Eleven lesions proved to be malignant, either primary lung cancer or metastases from prior malignancies. Five lesions turned out to be benign. Mean procedural time for marking wire placement was 35min; mean VATS duration was 36min. There is a learning curve for the whole team involving anesthesiology, radiology, and thoracic surgery. Conclusion: CATS is a new, safe, and effective procedure for minimally invasive marking of small, deeply-located intrapulmonary lesions. The benefits of CATS are: (1) ‘one-stop shopping’ procedure to locate and remove small lung lesions (2) lower risk for the patient (no patient relocation intraoperatively, no marking wire loss), and (3) no necessity to coordinate scheduling between CT and operating theatre.

Keywords: screen-detected lung cancer, Video-assisted thoracic surgery, cone-beam CT, guide-wire placement

P3.04-009 PHOTODYNAMIC THERAPY (PDT) TURNS 21: INDICATIONS, APPLICATIONS AND OUTCOMES FOR NSCLC
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Background: Photodynamic therapy (PDT) remains a novel ablative modality for managing NSCLC as it enters its 21st year since FDA approval. Initially proposed for definitive management of early NSCLC and palliative control for advanced NSCLC, PDT has grown beyond the limited indications to find broad applications in the spectrum of thoracic disease. This report details indications, applications, and outcomes from 2 centers with active PDT programs. Methods: Patients treated with PDT between 1998 and 2016 were entered retrospectively (prior to 2012) or prospectively (after 2013) into an IRB approved registry. All patients received a single photosensitizer, Photofrin, at a dose of 2 mg/kg IV. PDT was accomplished with lasers delivering light at 630 nm. Dosimetry ranged from 100-200 J/cm2. We defined a course of therapy as all light applications administered after a single injection of photosensitizer (range 1-3). Demographics, procedural details, clinical indications, clinical course and outcomes data were entered into the registry. These records were evaluated for this review. Results: Our programs treated 812 patients with PDT; there were 210 females and 602 males. The age at treatment ranged from 21 to 91. We treated 458 patients with bronchogenic carcinoma. The stages included: stage 0 (5), stage I (48), stage II (38), stage IIIa (82), stage IIIb (97) stage IV (176), 333 (82%) patients were managed with a single course of PDT; 65 patients were treated with multiple courses of PDT ranging from 2-6 times. Symptom management and palliation accounted for 63% of the indications. The majority of patients were treated with curative intent as part of a multimodality regimen. Photodinamics was <1%. There were no airway perforations. There was 1 bronchial stricture which resolved after a single course of PDT in a previously resected but not radiated patient. Conclusion: PDT for NSCLC is applied most often for advanced stage (3b/4) disease for management of airway symptoms. PDT can be used as a single definitive therapy for early stage disease and can be incorporated safely into a multimodality regimen which may include surgery, radiation and chemotherapy. Photosensitivity and airway injury are rare. Twenty one years after achieving FDA approval, PDT continues to have a place in managing patients with NSCLC. The favorable safety profile, compatibility with other therapies, and repeatability of courses of therapy suggest that we evaluate additional ways to apply PDT as endoscopic technology provides enhanced access to the airway and peripheral lung parenchyma.

Keywords: bronchoscopy, photodynamic, laser

P3.04-010 CHANGES OF RIGHT LUNG VOLUME AFTER RIGHT UPPER LOBECTOMY FOR LUNG CANCER
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Background: Many surgeons routinely perform the division of the inferior pulmonary ligament (IPL) during the right upper lobectomy for lung cancer. It is believed that the division of the IPL can facilitate mobilizing and expanding residual lobes, and decreasing resection and space. We aimed to evaluate the volume changes of the right middle lobe (RML) and the right lower lobe (RLL) after upper lobectomy according to IPL division. Methods: We performed a retrospective analysis of the medical records and images of 181 patients with lung cancer who had underwent right upper lobectomy via a video-assisted thoracic surgery (VATS) in Seoul Asan Medical Center from May 2009 to December 2013. The IPL was preserved in 76 patients (Group A) and was divided in 105 patients (Group B). In-house software with chest computed tomography (CT), we compared the difference volume changes of pre- and post-operative RML and RLL between the two groups. Results: There were no significant differences between the two groups in terms of age, sex, height, tumor size, chronic obstructive pulmonary disease and smoking status. In group A, the adjusted mean volume change of difference RML (dRML) and difference RLL (dRLL) were -0.45 mL/kg and 6.03 mL/kg, respectively. In group B, the adjusted mean volume change of dRML and dRLL were -0.55 mL/kg and 5.28 mL/kg, respectively. The difference was not significant. Conclusion: Division of the IPL during the right upper lobectomy is not beneficial technique regarding remnant lung volume.

Keywords: lung volume, inferior pulmonary ligament, Right upper lobectomy
Background: Although the incidence of bronchopleural fistula (BPF) has decreased in past years, it remains a serious complication following pulmonary resection. Methods: Between 1999 and 2011, 865 patients with lung cancer underwent radical surgical resection. 732 (86.6%) males and 133 (15.4%) females were ranging between 22 and 79 years (average 55.2±8.1). We retrospectively reviewed the data for morbidity, mortality and complications, especially with regard to the type of bronchial suture. Results:

<table>
<thead>
<tr>
<th>Type of bronchial suture</th>
<th>Total cases</th>
<th>BPF (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hand closure</td>
<td>161</td>
<td>0.7%</td>
</tr>
<tr>
<td>Stapled closure</td>
<td>514</td>
<td>4.7%</td>
</tr>
<tr>
<td>Stapled closure with additonal hand suture</td>
<td>210</td>
<td>6.7%</td>
</tr>
<tr>
<td>Total</td>
<td>865</td>
<td>4.5%</td>
</tr>
</tbody>
</table>

All patients underwent radical operations: 286 (33.3%) pneumonectomies, 501 (57.9%) lobectomies and 78 (9.0%) bilobectomies. In postoperative period 39 patients (4.5%) had complication – bronchopleural fistula. After pneumonectomy BPF took place in 33 (11.5%), cases, not differing significantly from the volume of lymph node dissection. After lobectomy BPF occurred statistically significant rare – in 6 (1.0%) cases. It should be noted, that the volume of lymph node dissection not significantly affect the frequency BPF. The most frequently BPF occurred after pneumonectomies – 33 (26 on the right, 7 left). After lobectomies BPF occurred in less cases – 6 (2 on the right, 4 left). By using hand closure BPF occurred in 1 out of 141 (0.7%) cases. By using stapled closure – in 14 of 210 (6.7%). By using stapled closure with additional hand suture – in 514 (4.7%). Conclusion: Thus the safer technique of bronchus closure is hand suture. The stapled closure statistically significant increase the amount of BPF (p<0.05).

P3.04-014 SURGICAL OUTCOME AND DIAGNOSIS OF CN1 LUNG CANCERS AFTER INTRODUCING PET/CT

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Background: The mainstay of therapy for CN1 lung cancer is surgery; however, the pre-operative radiologic assessment of CN1 lung cancer remains challenging and it has been reported that approximately 30% of CN1 cases are pathologically pN2. The aim of this study was to determine the pre-operative evaluation and outcomes of patients with CN1 lung cancer. Methods: A prospectively-collected institutional database was used. In the current study, CN1 was defined as hilar lymph nodes 1 cm in the short axis on CT and standardized uptake values > 2.5 on PET/CT. Between January 2004 and March 2016, a total of 1082 lung cancer patients underwent surgery. After excluding patients who received pre-operative treatment or had an incomplete resection, 86 (7.9%) CN1 patients were retrospectively studied. We compared the characteristics and prognosis of CN1 patients with 783 (72.4%) CN0 patients. Because the patients with CN1pN2 were underestimated, we investigated the frequency and predictive factors for CN1pN2. Results: The median follow-up time was 68 months. Compared with CN0 patients, the proportion of males, smokers, and squamous cell carcinomas was higher in CN1 patients (p<0.01). In addition, CN1 patients had elevated CEA levels and increased SUV on PET/CT. Lymph node metastases were noted as follows: CN1pN0, 32 (37.2%); CN1pN1, 37 (43.9%); CN1pN2, 17 (19.8%); CN0pN0, 701 (89.5%); CN0pN1, 50 (6.4%); and CN0pN2, 32 (4.1%). Lymph node metastases were underestimated in 99 CN0 and CN1 patients (11.4%). The incidence of CN1pN2 was higher in CN1 cases (p<0.01). The 5-year overall survival of the underestimated cases was as follows: CN1pN2, 18.0%; CN0pN1, 63.7%; and CN0pN2, 39.5%. Among the underestimated cases, survival of CN1pN2 patients was significantly reduced (p<0.01). In addition, univariate analysis showed that smoking (p=0.04) and peripheral tumors (p<0.01) were predictive factors for CN1pN2. Multivariate analysis confirmed that CN1 peripheral tumors tended to be pN2. In 64 cases with peripheral tumors and n1, 14 (31.8%) were pN2. Conclusion: PET/CT can decrease the number of underestimated patients with CN1 lung cancer. Amongst CN1 lung cancer patients, pN2 existed in approximately 20% of cases. Especially, since around 30% of peripheral tumors with CN1 were pN2, invasive staging would be warranted before the treatment.

Keywords: Lung cancer N1 PET/CT Prognosis
Background: In Japan, the incidence of postoperative cerebral infarction in lung cancer is approximately 0.9%. Reportedly, carotid artery arteriosclerosis reflects arteriosclerosis in the whole body. We aimed to assess whether carotid ultrasonography contributes to the prevention of cerebral infarction and cardiovascular events in postoperative lung cancer patients, and identify preoperative factors for its indication. Methods: We analyzed 1418 consecutive patients with NSCLC who underwent surgical resection at Kyushu Medical Center between 1994 and 2014. Between 1994 and 2000 (first event), 334 patients with NSCLC did not undergo carotid ultrasonography. From 2001 and on (second event), 1084 consecutive patients underwent carotid ultrasonography. In cases of moderate or severe carotid artery stenosis, we used heparin infusion as cerebral infarction prevention. Results: At the first event, postoperative cerebral infarction occurred in four patients (1.2%) who did not present preoperative carovascular episodes. At the second event, four patients (0.36%) of 1084 patients presented postoperative cerebral infarction. We analyzed 130 patients (12.0%) of 1084 patients with over 30% carotid stenosis. Only 13 (10%) of 130 patients had preoperative cerebral infarction and 117 (90%) of 130 patients did not present preoperative carovascular episodes. All 130 patients were aged ≥51 years. In total, 78 (46.6%) patients with mild to severe stenosis (linear internal carotid artery [ICA] 30%–99%), 56 (63.0%) patients with moderate stenosis (linear ICA 50%–69%), and 16 (12.4%) patients with severe stenosis (linear ICA >70%) were identified. The stenosis rate increased with age. Severe stenosis was identified in 16 patients, of which 15 had no preoperative carovascular episodes. At the second event, there were 74 (6.8%) cases of preoperative cerebral diseases; 303 (28.0%), hypertension; 72 (6.6%), coronary artery disease; 11 (1.0%), arrhythmia; 19 (1.8%), peripheral vascular diseases; 14 (1.3%), abdominal aortic aneurysm; and 121 (11.2%), diabetes mellitus. There was a significant correlation between carotid stenosis and hypertension and smoking and diabetes mellitus and smoking (p<0.001). The incidence of postoperative carovascular morbidity was 25 (7.4%) and 26 (2.3%) at the first and second events, respectively. There was a significant difference between the two occurrences of postoperative cerebral infarction (p=0.008) and cardiovascular complications (p=0.001). Conclusion: Carotid ultrasonography is recommended for patients aged above 50 years, with hypertension and smoking, and diabetes mellitus and smoking. Even without past cerebral infarction, the likelihood of carotid artery stenosis is high with increasing age. Carotid ultrasonography is simple, noninvasive, and useful as a preoperative assessment for preventing postoperative carovascular complications in lung cancer patients.

Keywords: Postoperative carovascular complication, Prevention of postoperative cerebral infarction, Preoperative management, Carotid ultrasonography

P3.04-017 WEDGE RESECTION FOR CLINICAL-N0 NON-SMALL CELL LUNG CANCER
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Background: Sublobar resection is generally indicated for small ground-glass opacity (GGD)-dominant clinical T1 adenocarcinomas below 2 cm in diameter. Recently, some reports show that GGD-dominant clinical T2 adenocarcinomas measuring below 3 cm are also favorable prognosis after segmentectomy. The aim of this study was to evaluate the prognosis of the patients with non-small cell lung cancers after wedge resection. Methods: From 2008 to 2012, 66 patients underwent wedge resection for clinical-N0 lung cancer at Kyoto Prefectural University of Medicine. Patients who had multiple tumors or previously underwent lung surgeries were not included. The median age of the subjects was 72.0 years. High-resolution computed tomography (HRCT) was performed for preoperative staging of the entire lung cancer. The median tumour size was 2.2 cm. All tumours were evaluated to estimate the GGO on HRCT. We defined the ratio of the maximum diameter of the consolidation to the maximum tumour diameter as the consolidation-to-tumour ratio (CTR). Analysis of the proportion of patients who underwent wedge resection were followed up with HRCT every 6 months for the first 2 years and every 12 months for the subsequent 3 years. The median postoperative follow-up period was 41.5 months. The Kaplan-Meier method was used to assess recurrence-free survival (RFS) and 5-year overall survival (OS), which were statistically analyzed using the log-rank test. We set the significant level at p<0.05. Results: Twenty two (33.3%) of the 66 patients had GGO-dominant tumours with CTR of less than 50%, and have survived without recurrence. The 5-year OS, RFS and CSS of whole patients were 66.1%, 53.4% and 81.6% respectively. The 5-year OS significantly differed according to CTR and solid tumour size. The 5-year RFS significantly differed according to CTR, solid tumour size, CEA level, and histological type. No significant differences in sex, whole tumour size and Brinkman index were observed. Multivariate Cox proportional hazard model revealed that solid tumour size and CTR were independent prognostic factors for OS, RFS and CSS. Lung cancer death accounted for 70% of the 20 cause of death, leading cause of death of remaining half was 7 other malignant tumours. 18 patients experienced a recurrence of lung cancer. Site of recurrence was 8 lung parenchyma including 2 stump recurrences, 8 mediastinal lymph node, 4 pleural dissemination and 4 distant organ. Conclusion: A solid tumour size ≥3 cm and CTR ≥50 might be a good, radiologically objective indicator for performing wedge resection of clinical-N0 non-small cell lung cancer.

Keywords: solid tumor size, wedge resection, non-small cell lung cancer, consolidation tumour ratio

S732
P3.04-018 RECURRENCE DYNAMIC OF COMPLETELY RESECTED NON-SMALL CELL LUNG CANCER IN PERSPECTIVE OF FOLLOW-UP SURVEILLANCE
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Background: There is no clear evidence or consensus on the modality and frequency of follow-up surveillance after complete resection of non-small cell lung cancer (NSCLC). Understanding of recurrence dynamic is essential to establish more efficient surveillance strategy. We investigated recurrence dynamic in completely resected NSCLC to propose a reasonable surveillance strategy. Methods: A total of 950 patients who underwent complete resection of NSCLC from 2006 to 2019 were reviewed retrospectively. Clinic-pathological data including follow-up surveillance records were obtained. All patients were completely followed until October 2015. Pathologic stage I, II, and IIIa NSCLC were included in the analysis. Mode of detection and the chronological pattern of recurrence were analyzed. Results: The median follow-up duration was 72 months. Recurrences were detected in 259 patients (27.2%) and freedom-from-recurrence rates were 78.2% at 2 year and 69.9% at 5 year. Recurrence was detected by routine follow-up study in 227 (88.5%), and by symptoms in 32 (12.7%) patients. In 65.5% patients, recurrence was detected by computed tomography and 26.2% was detected by positron emission tomography. The median time-to-recurrence was 1.1 year in entire recurrence group. Median-time-to-recurrences were 1.5 year in stage I (106), 1.9 year in stage II (61), and 1.1 year in stage III (92). There was no significant difference in chronological trend between the three stages (p=0.26). The cumulative rates of recurrence were 41.7%, 73.8%, and 91.1% at the 1st, 2nd, and 3rd year. Chance of recurrence dropped below 5% after 3 years and the probability of detection of recurrence was 8.6%. (Fig1)

Conclusion: Chronological patterns of recurrence of NSCLC does not different between stages and majority of recurrences were detected within postoperative second year. The probability of recurrence were significantly reduced after second year regardless of stage. Intensive surveillance until postoperative second year and less intensive surveillance from third year is a reasonable strategy.

Keywords: Surgery, Surveillance, non-small cell lung cancer, recurrence dynamics

P3.04-019 NODAL UPSTAGING IN CNO LUNG CANCER IS MORE INFLUENCED BY TUMOR SIZE THAN THE SURGICAL APPROACH
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Background: Several studies reported a lower rate of nodal upstaging in patients undergoing Video-assisted-thoracoscopic-surgery (VATS) anatomic resections compared to patients treated with an open resection. Aim of this analysis was to investigate nodal upstaging in cases treated by VATS or an open approach and to delineate predictive factors in a large consecutive cohort of patients. Methods: NSCLC patients with cN0 status treated between 2004 and 2015 were included in this retrospective analysis. Tumors were reevaluated with regards to tumor location: a tumor was classified “central”, if it had contact to the main bronchus or first segmental branch in a CT scan or was visible during bronchoscopy. All others were classified “peripheral”. VATS was introduced in 2009, since that time all clinically nodal negative patients were treated with an intended VATS approach. Results: Surgery was performed in 370 CNO patients: 257 (69.5%) VATS and 113 (30.5%) open resections. 49 lesions (13.2%) were classified as central tumors. Nodal upstaging was detected in 73 (19.7%) patients. The rate of upstaging was 19.3% and 21.2% in VATS and open resection, respectively (p=0.629). There was significantly more upstaging in centrally located tumors with thoracotomy (33.3% vs. 10.3%, p=0.045). No difference was found in peripherally located tumors (18.5% vs. 20.2%, p=0.73). CT stage was significantly higher in thoracotomy patients (p<0.001) and was also associated with a higher rate of upstaging. No difference between VATS and open resection was observed in the different tumor stages (CT1: 14.7% vs. 10.9%, p=0.478; CT2: 30.5% vs. 27.1%, p=0.698; CT3: 28.6% vs. 50, p=0.285). However, there was a trend towards larger tumorsize in centrally located tumors with thoracotomy (p=0.062). Conclusion: According to our analysis VATS is not associated with reduced rates of nodal upstaging. CT status was a predictive factor for nodal upstaging. The higher rate of nodal upstaging in centrally located tumors with open resection might be biased by a larger tumor size.

Keywords: upstaging, VATS

P3.04-020 SEGMENTECTOMY IN PATIENTS WITH PULMONARY MALIGNANCIES USING 3D-CT RECONSTRUCTION AND BRONCHOVASCULAR SEPARATION
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Background: Progress in diagnostics and surgery in thoracic oncology is associated with increasing number of patients-candidates for sublobar anatomic pulmonary resection. Vascular variability of pulmonary segments anatomy requires special tools for individual preoperative planning. Methods: 84 patients who underwent segmentectomy due to low pulmonary function, severe comorbidity, previous history of lung resection and metastatic lesion were included in the retrospective trial from prospectively collected database. Inclusion criteria were clinical T1aN0M0 peripheral non-small cell lung cancer (NSCLC) measuring ≤2 cm (n=23) and resectable pulmonary metastases not suitable for wedge resection due to deep parenchymal location (n=61). Segmentectomies were divided into typical (where parenchymal division involves 2 planes) and atypical (more complex and technically demanding, when the segmental exclusion involves 3 planes). 19 patients underwent VATS segmentectomy. Three-dimensional computed tomography (3D-CT) with bronchovascular separation was used preoperatively in 32 patients from October 2014 to May 2016. Mortality, morbidity, proportion of typical versus atypical and VATS versus open segmentectomies in two groups: with or without 3D-CT bronchovascular reconstruction, were compared. Results: There was no mortality in whole group. Morbidity rate was 14% not exceeding grade 3a according thoracic mortality and morbidity (TMM) score. The difference in morbidity rate was not statistically significant between two groups (15.3% and 12.5%, p=0.64). The most common complication was prolonged air leak for 7 days (8%). 3D-CT powered by separation of arterial, venous and bronchial structures enabled surgeons to perform atypical segmentectomies and use VATS approach more often (37% vs 4% and 42% vs 16%, respectively). 7 atypical segmentectomies were performed by VATS due to 3D-CT reconstruction with bronchovascular separation. Conclusion: 3D-CT reconstruction with bronchovascular separation provides precise preoperative planning of individual pulmonary segments anatomy and enables to increase the proportion of atypical and VATS sublobar anatomic pulmonary resections.

Keywords: segmentectomy, 3D reconstruction, pulmonary neoplasm
P3.04-023 PERIOPERATIVE MANAGEMENT OF ANTIPLATELET THERAPY IN PATIENTS WITH CORONARY STENT WHO NEED THORACIC SURGERY

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Background: Guidelines recommend delaying noncardiac surgery in patients after coronary stent procedures for 6-12 months after drug-eluting stents (DES) and for 6 weeks after bare metal stents (BMS). It is often replaced by bridging heparin for the prevention of perioperative stent thrombosis. We investigated the perioperative outcomes between patients with and without the discontinuation of antiplatelet therapy.

Methods: We performed thoracic surgery with antiplatelet therapy (APT) or bridging heparin in perioperative management for patients with coronary stent. We investigated the perioperative outcomes between the patients with and without the discontinuation of antiplatelet therapy.

Results: Males were 13 cases (76%) and female were 16 cases (24%). The type of stent was drug-eluting stent (71%), and bare metal stent (29%). The type of surgery was lobectomy (49%), pneumonectomy (21%), and other (30%). There was no difference in perioperative complication between the patients with and without the discontinuation of antiplatelet therapy.

Keywords: Thoracic surgery, coronary stent, antiplatelet therapy, perioperative management.
cancer. However, the patients who have poor lung function or small size lung nodule underwent sublobar resection. We retrospectively reviewed the oncologic outcome after sublobar resection lobectomy in stage I and II non-small cell lung cancer. Methods: 1019 consecutive patients who underwent lung resection surgery due to non-small cell lung cancer between January 2000 and December 2009 were evaluated through retrospective chart review. We used the Kaplan-Meier method to examine survival and recurrence, Cox proportional hazard model to identify variables affecting survival and recurrence. Results: We performed lobectomy in 928 patients, while sublobar resection in 90 patients. 5-year survival and 10-year survival were not shown statistically significant between sublobar resection and lobectomy (77.0% vs. 80.7%, 58.5% vs. 62.1%, p=0.566). 5-year and 10-year disease free survival were not also shown the difference between sublobar resection and lobectomy (68.9% vs. 63.8%, 67.8% vs. 57.8%, p=0.246). Univariate analysis using the Cox proportional hazards regression model identified sublobar resection is not predicting factor for recurrence (p=0.246). Conclusion: Our results suggest that the oncologic outcome of sublobar resection versus lobectomy is not significant difference in stage I and II non-small cell lung cancer patients. These results will be validated by prospective randomized trial.

Keywords: lobectomy, non-small cell lung cancer, sublobar resection

P3.04-025 REPEATED LUNG RESECTION OF IPSILATERAL LUNG CANCER THAT IS DETECTED AFTER SEGMENTECTOMY FOR PRIMARY LUNG CANCER
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Background: Small peripheral lung cancer has increasingly been treated by segmentectomy as a limited resection for both curative and compromised intent. Few reports have described repeated resection of a new lesion originating in the lung of same side during postoperative follow-up. Methods: We experienced five cases of repeated ipsilateral lung resection after segmentectomy. Clinicopathological data and operative procedure were analyzed retrospectively. Results:

The reason of limited resection for the first lung cancer was compromised intent in three cases and curative intent in two cases. Median time to second operation after initial resection was 63 months (20 to 106 months). Preoperative pulmonary function test before repeated operation was normal in all cases. In four cases, location of second cancer was in the same lobe of the first cancer. Procedure of repeated resection was partial resection in one, segmentectomy in two, completion lobectomy in one and completion pneumonectomy in one. All tumor were resected completely. There was no morbidity nor mortality. Histopathological diagnosis of second cancer was surgical-margin recurrence in two, second primary cancer in three. All cases except partial resection required intapericardial vascular exposure due to severe adhesion around pulmonary artery and vein. Among five cases, completion lobectomy of the left upper lobe was the most difficult surgery due to adhesion between pulmonary artery and bronchus. Conclusion: Repeated resection of ipsilateral lung cancer detected after segmentectomy was undergone safely. The difficulty of the procedure depends on the location of the tumor and the type of procedures.

Keywords: segmentectomy, repeated lung resection, primary lung cancer

Poster Session 3 - P3.04 - SURGERY

P3.04-026 A SIMULTANEOUS SURGICAL STRATEGY FOR PATIENTS WITH LUNG CANCER AND SEVERE CARDIAC DISEASES REQUIRING SURGICAL TREATMENT
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Background: The simultaneous surgical treatment of lung carcinoma and cardiac disease is rare. The aim of the study was to analyze the early and midterm results of simultaneous surgical treatment for concomitant lung cancer and cardiac diseases which both needs surgical treatment. Methods: We performed a retrospective review of 12 patients who underwent pulmonary and cardiac surgery, from 2002 to 2015, in a single institution. We focused on early postoperative morbidity and mortality. Results: Total 12 patients were recruited from 2002 to 2015 in the department of cardiothoracic surgery at the Samsung Medical Center in Korea. Nine patients were the diagnosed as concomitant non-small cell lung cancer and coronary artery disease, one patient was diagnosed as concomitant non-small lung cancer and aortic arch aneurysm, one patient was diagnosed as concomitant non-small lung cancer and mitral stenosis with tricuspid regurgitation, one patient was diagnosed as concomitant BALToma and ASD with pulmonary hypertension. Various cardiac surgeries were performed simultaneously with the pulmonary resection. Ten patients were performed via median sternotomy, and 2 patients were performed via anterior thoracotomy. The mean age of the patients was 62.7 years old. Follow-up ranging from 6 months to 12 years is available for these patients. The lobectomy by median sternotomy rate was 41.6% (5 patients), thoracotomy by anterior thoracotomy rate was 36.7% (2 patients), and the wedge resection by median sternotomy rate was 41.6% (5 patients). There were no mortality or major morbidity, apart from 8 minor complications in four patients (33.3%) (air leak, atrial fibrillation, atelectasis, pneumonia, delirium). Conclusion: Simultaneous cardiac surgery and lung resection in this small number of patients were safely performed without life-threatening morbidity and no in-hospital mortality.

Keywords: simultaneous surgery, lung cancer, cardiac disease

Poster Session 3 - P3.04 - SURGERY
critical adhesions around the CABG field, which need meticulous surgery. Keywords: CABG, lung cancer, Feasibility, Surgery

POSTER SESSION 3 – P3.04: SURGERY
MISCELLANEOUS I – WEDNESDAY, DECEMBER 7, 2016

P3.04-028 THE LEFT UPPER DIVISION SACRIFICE FOR BRONCHOPLASTY FOR AN ADENOID CYSTIC CARCINOMA OF THE LEFT MAIN BRONCHUS
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Background: The adenoid cystic carcinoma is sometimes growth in the upper airway. Main treatment for the disease is included operative resection and radiotherapy. The operative resection often needs air way reconstruction. We performed bronchoplasty and additional left upper division lung segmentectomy for the anastomotic tension to reduce for an adenoid cystic carcinoma patient of the left main bronchus. Methods: <Cases> 63 year-old male with severe Diabetes mellitus (HgbA1c level=10.4) was admitted to our hospital because of cough and sputum. Bronchosopic examination showed a tumor of the left main bronchus, and pathologic examination of transbronchial biopsy revealed adenoid cystic carcinoma. We performed 6 rings of the left main bronchial cartilage resection and bronchoplasty, and additionally, the left upper division segmentectomy were performed for reduction of the bronchial anastomotic tension. The bronchoplastic site was covered with the left thymic lobe between the left main pulmonary artery. Results: There was no severe complication after the operation. The pathological examination showed the no regional lymph node metastasis, however, the microscopic tumor positive of the both side bronchial stump. On the 48th day after the operation, he was applied of 60 Gy radioactive rays for the left main bronchus. On the 28 months after the operation, he is well without any tumor recurrence. Conclusion: We successfully performed the left main bronchoplasty for adenoid cystic carcinoma patient with severe Diabetes mellitus. The left upper division segmentectomy was useful for tension reduction of the bronchoplastic anastomosis.

Keywords: adenoid cystic carcinoma, bronchoplasty, segmentectomy

POSTER SESSION 3 – P3.04: SURGERY
Miscellaneous II – WEDNESDAY, DECEMBER 7, 2016

P3.04-029 A PROSPECTIVE RANDOMIZED TRIAL OF INTERMITTENT CHEST TUBE CLAMPING MAY SHORTEN POSTOPERATIVE HOSPITAL STAY AND FINANCIAL COSTS OF MEDICAL CARE IN PATIENTS WITH PRIMARY LUNG CANCER
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Background: The adenoid cystic carcinoma is sometimes growth in the upper airway. Main treatment for the disease is included operative resection and radiotherapy. The operative resection often needs air way reconstruction. We performed bronchoplasty and additional left upper division lung segmentectomy for the anastomotic tension to reduce for an adenoid cystic carcinoma patient of the left main bronchus. Methods: <Cases> 63 year-old male with severe Diabetes mellitus (HgbA1c level=10.4) was admitted to our hospital because of cough and sputum. Bronchosopic examination showed a tumor of the left main bronchus, and pathologic examination of transbronchial biopsy revealed adenoid cystic carcinoma. We performed 6 rings of the left main bronchial cartilage resection and bronchoplasty, and additionally, the left upper division segmentectomy were performed for reduction of the bronchial anastomotic tension. The bronchoplastic site was covered with the left thymic lobe between the left main pulmonary artery. Results: There was no severe complication after the operation. The pathological examination showed the no regional lymph node metastasis, however, the microscopic tumor positive of the both side bronchial stump. On the 48th day after the operation, he was applied of 60 Gy radioactive rays for the left main bronchus. On the 28 months after the operation, he is well without any tumor recurrence. Conclusion: We successfully performed the left main bronchoplasty for adenoid cystic carcinoma patient with severe Diabetes mellitus. The left upper division segmentectomy was useful for tension reduction of the bronchoplastic anastomosis.

Keywords: adenoid cystic carcinoma, bronchoplasty, segmentectomy

POSTER SESSION 3 – P3.04: SURGERY
MISCELLANEOUS II – WEDNESDAY, DECEMBER 7, 2016

P3.04-030 Examination of the relevance of prolonged air leakage after pulmonary resection for lung cancer and factors affecting delayed wound healing
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Background: The management of prolonged air leakage (PAL), a common complication that occurs in 8% to 26% of patients undergoing pulmonary resection, is difficult in many cases, and is also associated with other complications. Blood coagulation factor XIII (BCFXIII) is known to play a role in wound healing. However, little is known about the role of BCFXIII in the field of thoracic surgery. We examined the association between BCFXIII and PAL, chronic obstructive pulmonary disease (COPD) and PAL, and total protein (TP; an index of nutrition) and PAL. Methods: This study included 63 patients with primary lung cancer who underwent pulmonary resection in our institution and developed air leakage for at least 3 days postoperatively. All patients agreed to measurement of their plasma BCFXIII levels. BCFXIII, TP, and pulmonary function were measured within 1 month preoperatively. TP and BCFXIII were measured 5 days after surgery. The t-test was used for statistical analysis. Results: The mean duration of drainage was 6.3±3.2 days in patients with a postoperative BCFXIII level of >70% and 8.8±4.2 days in those with a postoperative BCFXIII level of >70%. Patients with postoperative BCFXIII ≤70% (n=11) required drain placement for a significantly longer period (p=0.049). The mean duration of drainage was 6.3±3.2 days in patients with forced expiratory volume 1.0% (FEV1.0%) ≤70% and 8.8±4.0 days in those with FEV1.0% >70% (n=51). Patients with FEV1.0% <70% required drain placement for a significantly longer period (p=0.038). Our analysis did not find a significant difference in the duration of drainage in relation to nutritional status in groups with postoperative TP ≤6.6 g/dl and >6.6 g/dl (n=35). However, the postoperative BCFXIII levels were significantly lower in patients with low postoperative TP levels (BCFXIII 79±16%) than in those with normal postoperative TP levels (BCFXIII 95±23%) (p=0.033). Conclusion: Our results suggest that low BCFXIII levels may be associated with PAL. Moreover, we found COPD to be closely related to PAL. No significant difference was noted in the duration of drainage between normal and low-nutrition patients. However, poor nutrition may have an effect on PAL as a result of decreased BCFXIII level.

Keywords: Blood coagulation factor XIII, Chronic obstructive pulmonary disease, prolonged air leakage

POSTER SESSION 3 – P3.04: SURGERY
MISCELLANEOUS III – WEDNESDAY, DECEMBER 7, 2016

P3.04-031 INTERMITTENT CHEST TUBE CLAMPING MAY SHORTEN CHEST TUBE DURATION AND POSTOPERATIVE HOSPITAL STAY OF LUNG CANCER SURGERY
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Background: Postoperative pleural drainage markedly influences the length of postoperative hospital stay and financial costs of medical care. Previous
report documented the safety of chest tube clamping before removal. This study aims to see if intermittent chest tube clamping might shorten chest tube duration and hospital stay of lung cancer surgery. Methods: From July 2012 to June 2016, 285 consecutive cases of operable lung cancer patients undergoing lobectomy and systemic mediastinal lymphadenectomy were retrospectively analyzed. Chest tube management protocol was modified since January 2014 according to the literature. Before that, patients (Group control, n=63) were managed with gravity drainage (water seal only and without suction). After that, patients (Group clamping, n=222) were managed with gravity drainage during first 24 hours after surgery (water seal only and without suction). Once a radiograph confirmed the reexpansion of the lung and no air leak detected, the tube would then be clamped intermittently at 24 hours after surgery and nurses checked the patients every 6 hours. If no abnormal symptoms developed (such as severe dyspnea, pneumothorax, subcutaneous emphysema), then unclamped 30 minutes to record drainage volume every 24 hours. The tube would be removed if drainage was normal and its volume was less than 200 mL in both group. All clinical data were recorded. Propensity score matching at 1.1 ratio was applied to balance variables potentially affecting chest tube duration between Group Clamping and Group Control. Analyses were performed to compare chest tube duration and postoperative hospital stay between the two groups. Variables linked with chest tube duration were gender, operation side, VATS and chylothorax, which were assessed using multivariable logistic regression analysis in whole cohort. Results. The rate of thoracocentesis after chest tube removal did not increase in Group Clamping compared with Group Control in whole cohort (0.5% vs. 1.5%, P=0.386). The rates of pyrexia were also comparable in two groups (2.3% vs. 3.2%, P=0.685). After propensity score matching, 61 cases remained in each group. Group Clamping showed shorter chest tube duration: (4.0 days vs. 4.8 days, P=0.001) and shorter postoperative stay (5.7 days vs. 6.4 days, P=0.025) compared with Group Control. Factors significantly associated with shorter chest tube duration were being female, left lobectomy, chest tube clamping, VATS and absence of chylothorax (P<0.05). Conclusion. This study suggests that chest tube clamping may decrease the length of chest tube duration and postoperative hospital stay while maintaining patient safety.

Keywords: lung cancer surgery, chest tube clamping, chest tube duration, postoperative stay

P3.04-032 STERNAL RECONSTRUCTION WITH A CUSTOM-MADE TITANIUM NEOSTERNUM AFTER RESECTION OF A SOLITARY BREAST CANCER METASTASIS

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Background: Bone is the most common metastatic site of breast cancer; and sternal metastasis usually occurs in an isolated setting. We report an extremely rare case of a patient who underwent subtotal sternal resection, followed by reconstruction using a new total titanium custom-made neosternum and the complete coverage of the surgical wound by latissimus dorsi flap suggest that these procedures may be useful in reconstructing large defects in the chest wall. Methods: A 47-year-old female with history of breast carcinoma and been given a left-sided conservative surgery 4 years ago with chemotherapy and radiotherapy. She’s presented with a progressively enlarging mass of her anterior chest wall and dull pain in the upper mid-chest. Computed tomography revealed an osteolytic lesion in the bone marrow of the sternum. The tumor extended across the destroyed cortex involving some of the costal cartilage and most of the sternal body. Diagnosis of invasive ductal carcinoma was made by echoed-guided core biopsy. 18-Fluoro-Deoxo-Glucose(FDG) positron-emission tomography (FDG-PET) showed hypermetabolic left breast mass with distant metastasis. Results. Sternal resection was performed successfully and a custom-made titanium neosternum was designed based on three dimensional simulation from preoperative chest computed tomography to reconstruct the anterior chest wall. Postoperative care was uneventful during a 10-day in-hospital stay. After a 6-month follow-up, the patient denied any shortness of breath, chest pain or limitation on her daily activities. The chest was stable without any paradoxical motion. Chest X-ray did not show any material dysfunction, pleural effusion or lung abnormalities. Conclusion: This new material used in our sternal reconstruction may extend the existing range of indications of sternectomy for cancer with curative intent.

P3.04-033 DIGITAL DRAINAGE SYSTEM REDUCES CHEST TUBE DURATION AND HOSPITALIZATION AFTER ANATOMIC PULMONARY RESECTIONS FOR MALIGNANCIES

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Background: The management of the chest tube after anatomic lung resections is critical to determine the length of stay and the cost of the hospitalization. New digital chest drainage systems promise to reduce the intervals to chest tube removal and to patient’s discharge from hospital. This study aims to compare the conventional water seal and the new digital drainage systems regarding chest tube duration and hospitalization. Methods: Between July 2015 and May 2016 consecutive patients submitted to elective pulmonary lobectomy, segmentectomy or biyectectomy for malignancies in the Cancer Institute of University of São Paulo (ICESP) used the digital drainage system Tho paz®. On the historic control group we included patients submitted to the same types of resection in our hospital between July 2014 and June 2015. All of them used the conventional water seal system. The groups were balanced for type of pulmonary resection and open versus minimally invasive techniques. Chest tubes were removed when the recorded airflow was less than 10 mL/min for the last 6 hours on the digital group and when there were no instantaneous air leaks during the daily rounds on the water seal group. The pleural drainage should be less than 400 mL/24 h for both groups. The patients were discharged from hospital according the same routine assistance protocols. Results: We included 110 patients. In each group, 50 lobectomies, 4 segmentectomies and 1 inferior bi-lobectomy were performed; thoracotomy was used in 19 patients in minimally invasive approaches in 36 cases per group. The groups were similar regarding gender (p=0.700), ASA Physical Status Classification System (p=0.838) and the Thoracic Surgery Scoring System (p=0.501). More patients had COPD in digital group (52.7%) than in water seal (30.9%) (p=0.033). Patients in the digital group were younger (median 65 years, IR:57-71) than in conventional group (median 70 years, IR:62-76) (p=0.016). The digital group had shorter chest tube interval (2 days, IR:1-4) than water seal (4 days, IR:3-5) (p=0.001). The same occurred on hospitalization: 4 days (IR:3-7) for digital and 5 days (IR:4-10) for conventional group (p=0.06). The morbidity was similar between groups, either for general (p=0.001) or for surgical complications (p=0.818). Conclusion: Patients undergoing anatomic lung resections for malignancies who were managed postoperatively with a digital drainage system experienced shorter chest tube duration and hospitalization, compared to those with conventional water seal drainage.

Keywords: Thoracic Surgery, Lobectomy, Chest drainage system, segmentectomy

P3.04-034 DIFFERENCES BETWEEN PLEURODESIS USING TALC AND SILVER NITRATE AT DIFFERENT TIMES OF PLEURAL DISEASE IN MICE

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Background: Recurrent malignant pleural effusion occurs in approximately 50% of patients with metastatic tumors and their therapy is essentially palliative. The most used method is the chemical pleurodesis. However, 50% of patients with metastatic tumors and their therapy is essentially palliative. The most used method is the chemical pleurodesis. However, we don't know what would be the ideal time to submit the patient to the procedure, neither what the best sclerosing agent. The objective is to analyze if the progression of the pleural neoplastic disease is associated with the degree of fibrosis in the pleura subjected to pleurodesis with talc and nitrate, in animals injected with 10 thousand Lewis’s cells intraperitoneal. Methods: In this experimental study we used twenty C56-BL mice, with pleural cancer induced by injection of 10.000 Lewis cells/ml of 0.9% saline. On the third day of pleural disease, half of the animals were subjected to pleurodesis, 5 of them with talc at a concentration of 400mg/kg(called Group 3 Talc “GT3”) and other 5 with silver nitrate in a concentration of 0.05%(called nitrato Group “GN3”). On the seventh day of pleural disease, the remaining subjects were again divided into 2 groups of 5 animals(GT7andGN7) and subjected to pleurodesis with the same substances and concentrations. All animals were sacrificed 7 days after
pleurodesis, regardless of which group they belonged. Results: All animals were pleural implants of cancer cells. Regarding the macroscopic findings were graded fibrosis in score been validated in other studies ranging from 0 (no fibrosis) to 4 (complete myofibrosis). In GT3 group, 2 animals had a score 2, and 2 animals obtained score 0.5. In the nitrate group (GN3) 3 animals had a score 0. In animals underwent pleurodesis after 7 days of illness, the talc group (GT7), 3 animals received a score of 0.2 and 2.5 respectively; the nitrate group (GN7) received scores of 0.5, 1 and 2. Microscopically, all had the presence of fibroblasts and fibrosis on pleural plaque. 2 blades each group (GT3 GN3, and GT7 GN7) were stained with picricus method for evaluating local fibrosis, and all had positive staining method including quantitation amount sufficient to further study. The animal control cutting blade, with only pleural disease had negative results. Conclusion: Animals with this number of implanted cells have sufficient survival and satisfactory answer to pleurodesis so we can quantify it according to the available methods. There was no weight loss or significant reduction in activity of the animals during time. Apparently, there is a greater amount of fibrosis in animals submitted to pleurodesis with talc.

Keywords: silver nitrate, pleurodesis, pleural effusion

POSTER SESSION 3 – P.04: SURGERY
MISCELLANEOUS II
WEDNESDAY, DECEMBER 7, 2016

P3.04-035 PLEURODESIS WITH A 50% GLUCOSE SOLUTION FOR POST-OPERATIVE PNEUMOTHORAX, AFTER CURATIVE LUNG CANCER RESECTION
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Background: Pleurodesis plays an important role in the management of pneumothorax, especially among patients who underwent curative lung cancer resection. Previous papers reported the efficacy of pleurodesis with OK-432, talc, or other cytotoxic agents, but these agents sometimes trigger lethal complications. Recently, several institutions reported 50% glucose solution as pleurodesis for pneumothorax. And we adopt it for post-operative pneumothorax patients. We report the feasibility of pleurodesis with 50% glucose solution for post-operative pneumothorax after curative lung cancer resection. Methods: From October 2014 to March 2016, 13 cases of post-operative pneumothorax after curative lung cancer resection were treated in our hospital. They were treated with pleurodesis with a 50% glucose solution. 200 mL of a 50% glucose solution with 10 mL of 1% lidocaine was instilled into the pleural cavity. Patients regularly change their positions for 2 hours, in order to disperse the pleural plaques. Pleurodesis was repeated until the air leak was stopped. Results: The subjects were 10 men and 3 women, with a mean age of 71 years. 9 patients were past or current smokers. All cases underwent video-assisted thoracoscopic surgery (VATS) lobectomy, and Right upper/middle/lower/Left upper/lower lobe resections were 5/2/2/1/2 cases each. Air leak stopped after pleurodesis in all cases, and 2 cases required repeated pleurodesis twice. No patient required re-operation, and was suffered from high fever, chest pain, or other complications. Drain tube was removed in 2.9 days after pleurodesis on average, and there was no post-treatment recurrence. Conclusion: These results demonstrated feasibility of pleurodesis with a 50% glucose solution for post-operative pneumothorax, after curative lung cancer resection. This procedure can be the first choice for post-operative pneumothorax treatment.

Keywords: pleurodesis, post-operative pneumothorax, Pneumothorax, 50% glucose solution

POSTER SESSION 3 – P.04: SURGERY
MISCELLANEOUS II
WEDNESDAY, DECEMBER 7, 2016

P3.04-037 RARE GIANT MALIGNANT TUMORS OF THE CHEST: RECONSTRUCTIVE CHALLENGE
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Background: In this article, we would like to present an unusual primary malignant tumors of the thorax. Case history and radiological studies of 4 patients with histologic diagnosis of thoracic sarcomas were interpreted retrospectively. Tumors originated from the chest wall, mediastinum, and pulmonary parenchyma. Histopathologic diagnoses were: thymo-liposarcoma, leiomyosarcoma, malignant Schwannoma and malignant mesothelioma – sarcomatoid type. In order to evaluate thoracic sarcomas, cross-sectional methods such as CT and MRI can be useful in demonstrating the origin of the mass, relationship with and involvement of adjacent structures. Chest wall resections are associated with significant morbidity, with respiratory failure in as many as 27% of patients. We hypothesized that our selective use of Dual-mesh prosthesis and STRATOS System (Strasbourg Thoracic Osteosyntheses) for chest wall reconstruction reduces respiratory complications. Methods: The records of all patients with giant tumors undergoing chest wall resection and reconstruction were reviewed. Patient demographics, use of preoperative therapy, the location and size of the chest wall defect, performance of lung resection if any, the type of prosthesis, and postoperative complications were recorded. Results: From February 2009 to January 2014, 4 patients underwent surgical treatment and chest wall resection for giant chest tumor. The median defect size was 80 cm² and the median number of ribs resected was 3. Lung resection was performed in 3. Prosthetic reconstruction was done with use of dual and polypropylene mesh and STRATOS system. Postoperatively, 1 patient died (had pneumonectomy plus chest wall resection. Respiratory failure did not occurred. Conclusion: Sarcomas are rare tumors of the thorax. They can originate from the lung parenchyma, mediastinum, pleura, or the chest wall. Angiosarcoma, leiomyosarcoma, rhabdomyosarcoma, and mesothelioma (sarcomatoid variant) are the most commonly encountered histopathological types. The diagnosis is established after making the differential diagnosis for histopathologically sarcoma-like malignancies (sarcomatoid carcinomas) and metastatic disease. Radiologically, these lesions usually appear as large heterogeneous masses. The use of malleable titanium bars to restore anatomic rib continuity helps to preserve the mechanics of ventilation better than a soft patch repair. We have no incidence of respiratory failure. Pneumonectomy plus chest wall resection should be performed only in highly selected patients.

Keywords: Sarcomas, Chest Tumors, Surgery

We retrospectively reviewed the records of patients with lung cancer who underwent surgery during April 2006 and March 2015 at our institution. Results: A total of 1,104 patients underwent pulmonary resection for primary lung cancer, and it included 45 patients with CTD (25 men and 20 women). The median age of patients with CTD was 69 years (range, 50-83 years). Thirty-two patients had rheumatoid arthritis, five had systemic sclerosis, five had dermatomyositis, two had systemic lupus erythematosus, and one had Sjögren syndrome. Further, 8 patients had interstitial pneumonia at preoperative imaging. 12 patients had obstructive pulmonary dysfunction, and 4 had restrictive pulmonary dysfunction. The distribution of patients according to cancer types was as follows: 27 had adenocarcinoma, 11 had squamous cell carcinoma, 1 had small cell carcinoma and 6 had other types. A total of 18 patients underwent thoracotomy, and 27 underwent VATS (5 wedge resection, 2 segmentectomy, 37 lobectomy, and 1 pneumonectomy). In all, 22 patients had pathological stage I A disease, 9 had stage IB, 3 had stage IIA, 3 had stage II B, 5 had stage IIIA, and 1 had stage IV. There was no significant differences in the pathological stage between patients with CTD and other patients (p = 0.76). The median follow-up period of patients with CTD was 32.6 months. No deaths occurred within 39 days post-surgery. The 5-year overall survival rate was lower in patients with CTD (68.6%) than in patients without CTD (74.0%) (p = 0.10). In univariate analysis, interstitial pneumonia was a prognostic factor (p = 0.0001). However, there was no significant difference in the existence of CTD (p = 0.10). Conclusion: Pulmonary resection in patients with CTD in our study was safe because of careful management during the perioperative period. Regular imaging follow-up for CTD enabled the early diagnosis of lung cancer, and postoperative prognosis was favorable.

Keywords: connective tissue disease, lung cancer, Interstitial pneumonia
POSTER SESSION 3 – P3.04 SURGERY
MISCELLANEOUS II – WEDNESDAY, DECEMBER 7, 2016

P3.04-038 PULMONARY RESECTION FOR METASTATIC PANCREATOBLIARY CANCER: CAN IT BE JUSTIFIED AS A TREATMENT OF CHOICE?
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Background: Patients with distant metastases of pancreaticobiliary cancers still have poor prognoses of 3-7% of 5-year survival, and the best reported median overall survival time (MST) of pancreatic carcinoma patients with metastatic stage IV disease treated with optimal chemotherapy was only 11 months. Surgical resection for metastatic lesions from pancreaticobiliary cancer is scarcely performed because of their malignant potential, therefore, few studies have reported on pulmonary metastasectomy for those patients. The purpose of this study is to review our experience of pulmonary resection for metastatic pancreaticobiliary cancer, and to assess whether this treatment offers them better survival. Methods: Between 2007 and 2015, 21 patients of pancreaticobiliary cancer had potentially resectable pulmonary metastases after definitive resection of primary site (pancreatic cancer, n=9; cholangiocarcinoma, n=10; gallbladder cancer, n=2). There were 14 males and 7 females with a median age of 67 years (42-87 years). The medical records were retrospectively reviewed, and the overall survival was analyzed. Disease-free interval (DFI) was defined as the time between operations for the primary cancer and the metastatic lesion. Results: The median DFI was 5 months (4-145 months), and 11 patients had solitary pulmonary lesion, 5 had double lesions, and 6 had three or more. Operative procedures of metastasectomy consisted of 15 wedge resections, 2 segmentectomies, and 4 lobectomies. Although no surgical complications and operative mortalities occurred, 9 patients died of primary diseases after pulmonary resection. The estimated MST after pulmonary resection was 35 months, and 3 and 5-years survival was 32% and 16%, respectively. Overall 3-year survival of patients with longer DFI (DFIs >36 months) was marginally significantly better than that of those with shorter DFI (DFIs 36 months) (49% vs. 19%, p=0.07). The longest survivor was still alive more than 5 years without recurrence after lung resection. Conclusion: Pulmonary resection for metastatic pancreaticobiliary cancer could be performed safely and might offer better survival. Although the optimal operative indication is still unclear, our results suggest that pulmonary resection could be a treatment of choice in selected patients with those diseases. Longer DFI before pulmonary metastasis might be helpful to select proper patients for the metastasectomy.

Keywords: Surgery, metastatic pancreaticobiliary cancer, metastatic pancreatic cancer, metastasis

POSTER SESSION 3 – P3.04 SURGERY
MISCELLANEOUS II – WEDNESDAY, DECEMBER 7, 2016

P3.04-039 SOLITARY FIBROUS TUMOR OF THE PLEURA ASSOCIATED WITH GYNECOMASTIA: A CASE REPORT
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Background: Fibrous tumor originated from pleura is a rarely seen lung tumor. It can be malignant or benign, and may cause paraneoplastic syndromes. Methods: In this study, we retrospectively evaluated a case in which a lung mass was detected during examination of the gynecomastia and operated in our hospital with the diagnosis of solitary fibrous tumor of the pleura. Results: A 53-year-old male patient was admitted to our clinic with the complaint of bilateral painful breast enlargement. Symmetrical gynecomastia with benign findings was detected in Category 2 level according to Breast Imaging Reporting and Data System (BI-RADS) classification in the bilateral breast ultrasonography investigations. Thorax computed tomography imagination showed extrapleurally located mass lesion with solid character and 75x25mm in size. Mesothelial cells were observed in the material received by the computed tomography-guided needle biopsy. Thereupon, a decision was made to take the patient to the operation. Frozen section procedure was performed on the specimen received by video-assisted thoracic surgery (VATS) biopsy. Diagnosis could not be achieved therefore it was decided to perform resection by mini-thoracotomy due to the size and rigid structure of the mass. During the process, it was observed that fibrous mass was holding the fat of the breast to a pedicle. It was found to be free in the other regions. The entire mass was removed with the resection including the surrounding healthy parenchymal tissue and the operation was terminated. The patient was discharged on the postoperative day 3. In the pathological examination, a solitary fibrous tumor associated with visceral pleura in the dimensions of 85x55x27 mm was reported with the features of low mitotic activity, and focal hypercellularity, and showing strong positive staining for CD34, CD99 and Bcl-2. In the additional investigations in gynecomastia clinics, it was observed that tumors were stained at 67.70% with progesterone and 35-40% with estrogen. Staining with H-Hcg was not observed. Conclusion: Solitary fibrous tumors of pleura is rare. These tumors originate from mesenchymal cells, not from mesothelial cells. These solitary fibrous tumors might be malignant or benign. These tumors may be asymptomatic, may cause symptoms of pressure or may lead to paraneoplastic syndromes. Recurrence can happen. Appropriate surgical intervention should be selected.

Keywords: solitary fibrous tumor, gynecomastia, pleura

POSTER SESSION 3 – P3.04 SURGERY
MISCELLANEOUS II – WEDNESDAY, DECEMBER 7, 2016

P3.04-040 A RARE CASE OF INTRATHORACIC MASS: INTRATHORACIC DESMOID TUMOR
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Background: Desmoid tumor is a rare type of tumor which originates from abdominal fascial and musculo-aponeurotic structure. It generally occurs in the abdomen, but rarely may be derived from the chest wall. Pain is the main complaint of the patients admitted to hospital. Methods: In this study, we retrospectively evaluated the pre-surgical diagnostic methods, surgical intervention and post-operative follow-up processes and outcomes of a patient who admitted to hospital with a complaint of back pain and were operated in our hospital with the diagnosis of desmoid tumor. Results: 57-year-old male patient was admitted to our clinic with the complaints of left arm and back pain suffered approximately more than 1 year. Due to the increasing pain and ptoisis in the left eye, imaging studies were performed and a mass was detected in the left hemithorax. Needle biopsy was applied to the patient two times but no results were obtained. Whereupon, the patient was referred to our clinic. During the physical examination of the patient in our clinic, a mild ptoisis in his left eye, palpable and hard fixed mass in the left supraclavicular fossa and loss of breath sounds in the upper left side of the hemithorax were detected. Thorax computed tomography imagination showed an extrapleural mass, 17x13x12 cm in size, which fills the superior and posterior mediastinum with the pleura. Additionally, a mass, 15x14x14 mm in size was reported with SUV upper value of 4.85, consisting with malignancy in the PET-computed tomography. Upon this, posterolateral thoracotomy surgery was applied to the patient and the mass was removed en bloc. The mass was reported as a desmoid tumor based on the pathological findings and the patient was discharged on the postoperative day 6. In the 3rd months follow-up process, 54 Gy / 30 fr radiotherapy was applied to the left hemithorax apical tumor location. In the control imaging studies following 3., 8., 24. and 30. months of the surgery, no lesion compatible with the recurrence was detected. Conclusion: Desmoid tumor is a rare type of tumor originating from abdominal fascial and musculo-aponeurotic structure. Surgical resection is needed. Because of the possibility of recurrence, surgical intervention should be modified in a way to remain the quality of patient's life.

Keywords: desmoid tumor

POSTER SESSION 3 – P3.04 SURGERY
MISCELLANEOUS II – WEDNESDAY, DECEMBER 7, 2016

P3.04-041 GIANT SOLITARY FIBROUS TUMOR OF THE PLEURA SAVED BY BIOPSY AND FOLLOWING EXTENDED RESECTION: A LONG TERM SURVIVING CASE
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Background: Giant tumor almost occupied the entire one-side thoracic cavity could be surgically resected completely is rare. Solitary fibrous tumor of the pleura (SFTP) is less common, giant SFTP, which could be surgically resected completely, could survive long term, is rare. Here we report one case giant SFTP. Methods: A male aged 39 in Dec 2008, with chest distress, fatigue and low-grade fever for 2 weeks, chest pain and dyspnea for 1 week, no bleeding sputum; chest CT revealed a giant tumor almost completely occupied the left upper lung.
the entire left-side thoracic cavity, with pleural effusion. Bloody pleural fluid was drawn but no malignant tumor cells was confirmed. Malignant mesothelioma was diagnosed at local hospital, not operable, no effective chemotherapy or radiation available. The patient was referred to our Lung Cancer Center. Biopsy was first advised. Biopsy pathology: SFTP (malignant). Surgical resection should be of the best choice even though the young patient seemed to be too fatigue to endure the large-incision traditional standard posterolateral thoracotomy (TSPT; 30–40cm long chest incision, with the latissimus dorsi and serratus anterior muscles being cut, usually one rib being cut). Results: Posterolateral incision was about 40cm long, S shape, with one rib cut, but the surgery space was still too limited to explore the giant tumor, to separate the intrathoracic adhesion. Incision was extended, and another rib was cut to enlarge the surgical field. The tumor occupied the whole thoracic cavity, bottom originated from visceral pleura of left apicalposterior (S1+2) and superior (S6) segments. Tumor 22cm×15cm×7cm was completely separated and en bloc resected, with S1+2 and S6 segments wedge-resected (cutting edges at least 2cm far from tumor). Postoperative pathology: SFTP (malignant). The patient recovered surprisingly quickly, drainage tube pulled out at 5th day, he was discharged at the 8th postoperatively. No adjuvant treatment was used. Follow-up shows no recurrence and metastasis. The patient is now alive healthily in his 8th year postoperatively, Conclusion: Giant SFTP is rare, easily to be misdiagnosed to malignant mesothelioma, losing opportunity of being cured. Biopsy is the key point to make a right diagnosis. Giant SFTP, benign or malignant, usually is operable; complete en bloc resection of the whole tumor and enough resection of originated visceral pleura and lung tissue is the key point to avoid recurrence, to cure SFTP. (This study was partly supported by Science Foundation of Shenyang City, China, No. F16-206-9-05). Keywords: traditional standard posterolateral thoracotomy, SOLITARY FIBROUS TUMOR OF THE PLEURA, biopsy

Results: In both cases we performed operation and found massive air leak coming out from holes on the bullae. We removed the bullae and stitched up leak points. We succeeded in reducing air leak at last. Their drains were removed in 2 weeks. Both of them are in good condition now. Conclusion: There are several similarities between these 2 cases. They had pulmonary emphysema but no bullae detected on preoperative CT. Recurrence of air leak after coughing triggered discovery of new occurring bullae, while postoperative air leak was being improved. It can be said that emphysema, improvement of air leak and coughing have something to do with onset of fast-growing bullae. We surgeons may have to keep in our mind the possibility of such occurrence, when we operate on similar patients as them. Keywords: fast growing, emphysematous bullae, after lobectomy, air leak
to use expensive thoroscopic devices, is very suitable for lung surgery in developing countries. (This study was partly supported by Science Foundation of Shenyang City, China, No. F16-206-9-05).

Keywords: sclerosing hemangioma of the lung, Minimally Invasive Small Incision, Muscle- and Rib-Sparing Thoracotomy, sclerosing pneumocytoma

P3.04-044 SURGICAL MANAGEMENT OF ARTERIOVENOUS MALFORMATIONS: OUR EXPERIENCE

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Background: Pulmonary arteriovenous malformations are rare lesions with significant clinical complications. These lesions are commonly seen in patients with hereditary hemorrhagic telangiectasia (formerly Osler-Weber-Rendu syndrome). Formerly called Osler-Weber-Rendu, HHT is an inherited disorder of the vasculature associated with AVMs and telangiectasias. Diagnosis of HHT is based upon the presence or absence of four specific clinical criteria often referred to as the Curacao criteria. Three criteria are present, the diagnosis is definite. If two criteria are present, the diagnosis of HHT is probable. If less than two criteria are present, the diagnosis is unlikely. Management of arteriovenous malformations (AVMs) remains challenging because of their unpredictable behavior and with high risk mortality. The purpose of this study was to review our experience with surgical management of arteriovenous malformations (AVMs). Methods: We diagnosed and treated a total of 11 patients with pulmonary arteriovenous malformation (PAVs). They have been admitted to the clinic with massive hemoptysis. Unknown initially diagnose. All patients are presented to hospital urgently with such clinical signs, epistaxis, cough, hemoptysis, weakness, sweat, fever, dyspnea, thoracic malaise, and massive right hemoptysis. But 3 patients with clinical signs of hemorrhagic shock with massive hemoptysis, tachycardia, weak pulse, hypotension, severe anemia. In one patient was presented with massive hemoptoxia after an episode of sudden shock. She was treated with right pleural drainage (average 2000ml) and intensive therapy and hemotransfusion (8 flacons). All patients are treated initially with intensive therapy and hemotransfusion and after that with hemodynamic parameters stable were treated with surgery. Patients were excluded with all the necessary of emergency examinations as thoracic radiography, biochemical examinations, CT scanner, MRI, Bronchoscopy, EKG, cardiac echo and cateterisation, gaseous exchange. Pulmonary angiography was performed in 8 patients. All patients were treated by surgical approach. Embolosclerosis was not definitive choice. Results: Arteriovenous malformation size ranged from 3.5 cm, on average (1-5 cm) and right lung location in seven patients, right lower lobe in 4 patients, middle lobe 1 patient, right upper lobe 2 patients. Location on left lung in 4 patients. In left upper lobe in one patient and left lower lobe in 3 patients. They were treated by lobectomy in 5 patients, anatomical segmentectomy in 3 patients, wedge resection in 3 patients. Morbidity 2 % and mortality in one patient Conclusion: Diagnosis and management of AVMS by surgical therapy resection was with very good results and with limited morbidity and low mortality and no recurrence during early follow-up. Keywords: Pulmonary arteriovenous malformation(PAVMs), hemorrhage hereditarie telangiectasia, lung resection

P3.04-045 PRIMARY LUNG CANCER PRESENTING AS PNEUMOTHORAX

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Background: Analysis of our patients with primary lung cancer presenting as pneumothorax Methods: Between 2010-2015 we treated in our clinic among 338 adults (258 men and 80 women) presenting with spontaneous pneumothorax, there were nine men and two woman with lung cancer: Seven squamous cell carcinoma, three adenocarcinoma and one oat cell carcinoma. Pneumothorax led to the diagnosis in 11 cases and the remaining occurred as a complication of known neoplastic disease. The average age was 60 years (32-72 years old). Results: We analyze these 11 cases treated in our hospital. In patients with normal chest X-ray film findings after lung resection, further investigation for neoplastic disease is not justified. But we need to perform and chest CT and other investigation in patients with, heavy smoking, chronic bronchitis, bullous emphysema and incomplete lung expansion after chest drainage also patients with age over 50 years old Conclusion: The occurrence of a pneumothorax in patients with lung cancer, worsening prognosis. Five-year survival is poor, suggesting that lung cancers present as pneumothorax at an advanced stage of disease. Keywords: chest X-ray, lung cancer, Pneumothorax

P3.04-046 CASES OF SURGICAL RESECTION OF POST-OPERATIVE LYMPH NODE RECURRENCES FROM PRIMARY LUNG CANCER

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Background: The prognosis of patients with recurrent nodal metastasis after resection of primary lung cancer is poor, and surgical resection is not indicated for patients with lymph node (LN) disease beyond N3. Recently, some reports showed the efficacy of surgical resection of the small number of distant metastases (oligometastasis). In our hospital, we had 7 cases of nodal metastasis resection after primary lung cancer resection. The purpose of this study was to discuss the possibility of improving prognosis by resection of nodal recurrence. Methods: From 2007 to 2013, we examined 7 patients for whom lymphadenectomy was performed to treat lymph nodal recurrence following curative resection of the primary cancer at our hospital. The mean age was 58 years (65-73 years), there were 2 females and 5 male patients. At the initial operation, there was 1 case of stageI, 3 cases of stageIIA, 3 cases of stageIIB, 4 cases of stageIIIA, 4 cases of stageIIIB, 1 case of stageIVB. Pathologically, there were 3 adenocarcinoma cases, 3 squamous cell carcinoma cases, and 1 adenosquamous carcinoma case. All patients underwent postoperative adjuvant chemotherapy, and 4 patients underwent postoperative radiotherapy for residual or recurrent tumors. Results: All 7 patients underwent lymphadenectomy; 3 had supracavicular recurrent LN and 4 had mediastinal recurrent LN. In 2 of the supracavicular cases and 1 of the mediastinal cases, the patients were alive without any recurrence. In the other four cases, the patients showed re-recurrence, received chemotherapy, and are alive. The median survival time from the day of recurrent lymphadenectomy was 32 months (27-52 months) and that from the day of the initial operation was 76 months (36-101months). The median disease-free survival time from the day of recurrent lymphadenectomy was 19 months (9-62months). The 2 years disease-free survival was 42.9%. The median interval from initial operation to recurrent lymphadenectomy was 43.3 months for the 3 cases without recurrence and 19.8 months for the 4 cases with re-recurrence. Conclusion: Complete cure or better prognosis could be expected via surgical resection for some cases with LN recurrence when the lesion is localized and has no distant metastasis. A longer interval between initial operation and the day of recurrence might indicate better prognosis. Therefore, surgical resection ofLN recurrence might be indicated if other metastatic lesions do not occur after a certain period. Keywords: recurrent nodal metastasis, lung cancer
Background: Recurrent laryngeal nerve (RLN) paralysis can occur following systematic upper mediastinal nodal dissection by radical surgery for primary lung cancer. However, there have been very few reports. Methods: We retrospectively reviewed the clinical data of 356 consecutive patients who underwent radical surgery for primary lung cancer with an over 6-month observation period in our institution from July 2010 to August 2015. There were 22 cases that experienced hoarseness after lung cancer surgery (6.0%). We could identify the movement of the vocal folds with a laryngoscope in 21 out of 22 cases (95.5%), because one patient refused to have the examination. Categorical variables were analyzed with Fisher’s exact test and continuous variables with the student’s t-test. P < 0.05 was considered statistically significant for all tests. Results: Hoarseness subsequent to radical surgery for primary lung cancer arose in 16 out of 308 (5.2%) cases of video-assisted thoracic surgery (VATS) including robotic VATS, in contrast with six out of 88 cases (6.8%) of open thoracotomy. All patients who experienced hoarseness had received upper mediastinal nodal dissection. Patients who had received right upper nodal dissection experienced hoarseness in eight out of 150 cases (5.3%), in contrast to 14 out of 84 cases (16.3%, P = 0.020) for left upper larynx nerve paralysis. Laryngoscopic examination revealed that five patients (23.8%) were diagnosed with right RLN paralysis and 15 (71.4%) as left. One patient who underwent VATS right upper lobectomy with upper mediastinal and subcarinal nodal dissection had left RLN paralysis. There was a patient (4.8%) who did not suffer from RLN paralysis, and one patient refused to undergo the examination. Eleven out of 18 patients (61.1%) were identified to improve the diagnosis of disorders of the vocal cords with the laryngoscope. It took one to 24 months (average 6.5 months) to improve the movement of the vocal cords observed with the laryngoscope. In addition, fourteen out of 19 cases (73.7%) were recognized for the improvement of their hoarseness. It took one to 24 months (average 10.4 months) to improve the voice disorder after surgery. Conclusion: In our cohort, 8.4% of patients who underwent systematic upper mediastinal lymph node dissection had hoarseness as a subjective symptom. However, 73.7% of patients who suffered from hoarseness and 62.5% of patients who were identified as having disorders of the vocal cords improved in more than two years.

Keywords: systematic mediastinal nodal dissection, hoarseness, recurrent laryngeal nerve paralysis, primary lung cancer

Poster Session 3 – P3.05: Palliative Care/Ethics
Symptoms, Therapeutic Interventions – Wednesday, December 7, 2016

P3.05-001 PSYCHOLOGICAL INTERVENTION TO TREAT DISTRESS AND SUFFERING EXPERIENCED BY PEOPLE WITH LUNG CANCER NEARING THE END-OF-LIFE

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Background: Despite advances in medical interventions, lung cancer continues to be associated with a poor prognosis with approximately 16% of people with lung cancer living five years post diagnosis. This poor prognosis can contribute to depression, anxiety, death anxiety and existential concerns and fears relating to meaning and purpose of life. There is a growing body of evidence indicating that behavioural and psycho-educational interventions are efficacious in treating depression and anxiety in lung cancer patients, however, little is known about how to psychologically treat suffering and distress near the end of life. Methods: A pilot search of PsychNFO and Medline was undertaken to identify existing and meaningful centered psychotherapies that were used towards the end-of-life with people with cancer. As the research in the area is in its infancy, all quantitative study designs and qualitative studies were included. Studies that focused on physical symptom management, dyspnea and bereavement interventions, measurement of psychological distress or existential concerns were excluded. Results: The search yielded a total of 62 articles, of which only 34 examined the use of psychotherapies towards the end-of-life care of people with cancer. The majority of these studies were focused on women with breast cancer, used structured outcome measures and were conducted very few, if any, participants with lung cancer. These studies identified and described at least 14 novel psychotherapeutic interventions that could be used towards the end-of-life. These interventions included: Legacy Activities, Life Review Therapy, Meaning-Centred Group Psychotherapy, Individual Meaning-Centred Psychotherapy, Dignity Therapy, Forgiveness Therapy, Meaning-Making Psychotherapy, Outlook Psychotherapy, Supportive Group Interventions, The Healing Journey Intervention, Cognitive Existential Interventions, Re-Creating Your Life Therapy, Mindfulness Interventions and Managing Cancer and Living Meaningfully. These interventions varied in the number of sessions and the level of training required to administer the interventions. Some of these interventions were manualized and others were less structured in their approach. Some of these interventions show potential in alleviating distress and suffering, improving life satisfaction, self-esteem and mood. Conclusion: There are only a small number of studies that evaluate the efficacy of psychotherapeutic interventions to be used with people with advanced cancer towards the end-of-life. Although results are promising it is difficult to conclude that one intervention is better than another. Further research is required to trial and adapt these interventions for use with people with lung cancer towards the end-of-life.

Keywords: Psychological Interventions, Existential distress, Therapies

Poster Session 3 – P3.05: Palliative Care/Ethics
Symptoms, Therapeutic Interventions – Wednesday, December 7, 2016

P3.05-002 MALNUTRITION IS AN INDEPENDENT RISK FACTOR ON SURVIVAL ON EGFR MUTATED PATIENTS DIAGNOSED WITH NON-SMALL CELL LUNG CANCER

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Background: Lung cancer continues to be the leading cause of cancer-related death worldwide. In Mexico, EGFR mutation is around 31%. Malnutrition is a common problem among patients with cancer, affecting up to 85% of end-stage cancer patients, and 50-56% advanced NSCLC patients. Malnutrition poses an unfavorable prognosis and has also been associated with higher incidence of treatment related toxicity. No evidence about malnutrition in EGFR mutated patients has been described. The objective of the study is to assess the relation between malnutrition and survival of patients with NSCLC and EGFR mutation. Methods: One hundred-five patients diagnosed with NSCLC EGFR mutation undergoing any line of treatment were assessed from January 2012 to June 2016. Malnutrition was measured using the Subjective Global Assessment tool (SGA), patients were classified as without malnourishment (SGA=A) or malnourished (SGA=B+C). Overall survival was compared with the Kaplan-Meier method. Results: Baseline characteristics are shown in Table 1. Table 1. 91.9% of patients were malnourished by the time of evaluation. Overall survival OS was 13.6 months (95% CI 12.7-14.4 months). Patients without malnutrition at the time of treatment initiation had a better OS than malnourished patients 14.2 vs 10.5 months (p=0.003) (Figure 1). Malnutrition is a risk factor for death independently of age, sex and treatment with TKIs versus chemotherapy (OR=2.7, 95% CI 1.01-75.4, p=0.049). Conclusion: Patients harbouring EGFR mutations benefit from more effective treatments, and usually have better prognosis. Malnutrition is an independent risk factor for mortality in this population, thus assessment of nutritional status and a timely referral to a nutrition expert could result a better prognosis and health related quality of life.

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Symptoms, Therapeutic Interventions – Wednesday, December 7, 2016

P3.05-003 ANXIETY AND DEPRESSION IN PATIENTS WITH EGFR+ NSCLC RECEIVING TREATMENT WITH TKIS

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Background: Patients with lung cancer (LC) report higher levels of anxiety and depression than cancer patients in general. Targeted therapies, such as tyrosine kinase inhibitors (TKIs) offer patients with EGFR mutations improved survival outcomes with less associated toxicity. This type of treatment has been associated with improvement on quality of life and lower symptomatic burden, which influence emotional status. The aim of this study is to report anxiety and depression prevalence and severity on patients with EGFR mutation on the course of the first four months of treatment with TKIs. Methods: A cohort of 76 LC patients receiving TKIs was evaluated. Hospital Anxiety and Depression Scale (HADS) and Quality of Life (QOL-30) scores were registered at baseline (T0), and after treatment (two cycles [T2] and four cycles [T4]). For each subscale of HADS, scores were rated: c7 as negative, 8-10 as low and 11-21 as severe. Score changes on emotional

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subscres were analyzed with Wilcoxon test. Results: Most patients reported normal levels of anxiety and depression at all times of the evaluation. Anxiety reduced significantly at T2 (p<0.007) and T4 (p<0.001). Depression rates remained stable, but were associated with worse global QoL scores (p<0.001), fatigue (p<0.01), emotional distress (p<0.001) and social distress (p<0.01). Conclusion: Anxiety and depression rates are highly prevalent in patients with EGFR mutations. The changes found on subscres scores may be due to several factors such as quality of life, performance status, response to treatment, a heightened perception of control and the expectation of having a better prognosis, among other factors. Since the needs of the patients vary according to treatment type, further studies on the emotional status of patients treated with novel therapeutic agents are warranted in order to understand factors that stimulate emotional well-being.

Keywords: Psychooncology, psychosocial, Anxiety, depression

Poster Session 3 – P3.05: Palliative Care/Ethics
Symptoms, Therapeutic Interventions – Wednesday, December 7, 2016

P3.05-004 Psycho-social Function and Caregiver’s Burden in Patients with Advanced Lung Cancer
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Background: Patients with advanced lung cancer (a-LC) are often characterized by high tumor burden and comorbidities that also correlated to anxiety and depression. The Authors report the preliminary results of a pilot experience on early simultaneous interdisciplinary palliative approach in a-LC patients, referring to the Thoracic Oncology outpatient department of a Clinical Cancer Center. The first aim of the study was to evaluate the quality of life and health status of these patients. Secondly, the caregiver’s burden of care has been investigated. Methods: 32 patients with a-LC (mean age 65 years; Standard Deviation (SD)=8.3) were enrolled. Psychological distress and health status were assessed by Hospital Anxiety and Depression Scale (HADS), and Short Form 36 Health Survey (SF-36). 23 caregivers (mean age 57 years; SD=14) compiled the Caregiver Burden Inventory (CBI) to evaluate their burden of care. Results: 55% of patients showed higher score in the total scale of anxiety and depression. 35% of caregivers reported higher level of burden. Among caregivers, women reported higher levels of feelings of fatigue (Physical Burden) as compared to men (F=4.45, p<0.05) that reported higher levels of Emotional Burden (F=7.25, p<0.05). The patient’s sons reported higher scores of Emotional Burden with respect to partners (F=4.75, p<0.05). Finally, younger caregivers showed higher scores about the Social (F=10.73, p<0.01) and Emotional Burden (F=26.6, p<0.01). The correlations among the questionnaires are shown in Table 1. Conclusion: In our sample of a-LC patients, psychological distress was correlated with general quality of life. The highest burden reported by caregivers was linked to the time dedicated to the assistance and to the feeling of fatigue. Our findings suggest to provide psychological support to caregivers, in particular for women to achieve a personal and private space, and for sons to the emotional management.

Keywords: Psycho-social function, caregiver’s burden, advanced lung cancer

Poster Session 3 – P3.05: Palliative Care/Ethics
Symptoms, Therapeutic Interventions – Wednesday, December 7, 2016

P3.05-005 Geriatric Assessment and Functional Decline in Patients with Lung Cancer
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Background: Physicians treating lung cancer are confronted with an expanding group of older patients. Treatment of these patients is complex and focuses on improving quality of life, maintenance of functional status (FS) and prolonging overall survival (OS). The present study aims to evaluate the role of geriatric assessment (GA) and the evolution of FS in older patients with lung cancer, and to identify predictors for functional decline and OS. Methods: Patients ≥70 years with a new diagnosis of lung cancer were included. At baseline, GA was measured, including functional status of Daily Living (ADL) and Instrumental Activities of Daily Living (IADL). ADL and IADL were reevaluated 2-3 months after diagnosis. OS was collected. Determination of predictors of functional decline on ADL and IADL and of OS was performed by univariate and multivariable logistic and Cox regression. Results: 245 patients with a median age of 76 years were included from October 2009 till January 2015. The majority of patients (58%) had stage IV disease. Treatment consisted of surgery in 20 patients (8%), radiotherapy in 105 patients (43%) and chemotherapy or targeted therapy in 125 patients (51%). At baseline, GA deficiencies were observed in all domains, most prominent for comorbidities (78%), fatigue (76%) and nutrition (76%). 240 patients (98%) had ≥210 abnormal domains with a median of 5. ADL and IADL impairments were detected in 51% and 63% of patients respectively. Follow-up ADL and IADL data were available for 145 patients. Functional decline for ADL was observed in 23% (95%CI 16.2, 29.9), and for IADL in 45% (95%CI 36.9,53.3) of patients. In multivariable analysis, radiotherapy was predictive for ADL decline. No other predictive factors for ADL or IADL decline were identified. In multivariable Cox regression, stage, gender and age were predictive for survival. Conclusion: Older patients with lung cancer are a high risk population with deficiencies in multiple geriatric domains. During treatment functional decline is observed in half of the patients, more prominently for IADL. Functional decline on ADL at 2-3 months is predicted by radiotherapy, possibly related to the acute toxicities of this treatment. None of the specific domains of the GA nor cumulative deficits on GA were predictive for functional decline or survival. Further research should focus on the role of interventions on evolution of quality of life.

Keywords: functional decline, older patients, Geriatric assessment, lung cancer

Poster Session 3 – P3.05: Palliative Care/Ethics
Symptoms, Therapeutic Interventions – Wednesday, December 7, 2016

P3.05-006 Anxiolytic Effect of Acupuncture in a Phase II Study of Acupuncture and Morphine for Dyspnoea in Lung Cancer and Mesothelioma
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Background: Background: Anxiolytics are commonly used in cancer patients. Treatment includes psychological therapies, psychotropic drugs and complementary therapies including acupuncture. Evidence for acupuncture for treating anxiety in cancer patients is lacking. Methods: A single-centre, randomised phase II study of patients with non-small cell lung cancer (NSCLC) or mesothelioma who assessed the use of acupuncture for control of dyspnoea. One-hundred and seventy-three patients were randomised to acupuncture alone (A), morphine alone (M) or the combination (AM). Acupuncture was administered at upper sternal, thoracic paravertebral, trapezius trigger points and thumb points (Li4). Manual semi-permanent acupuncture studies were inserted for patient massage when symptomatic. Arm A patients received rescue morphine. Results: There was no statistically significant difference in the dyspnoea control rate between arms. Secondary outcomes included measures of anxiety. The trial population had high levels of anxiety and depression with all patients having depression hospital anxiety and depression (HAD) score of >7 and 71.5% having anxiety HAD score of >7. VAS relaxation improved in arms A (1.06 points) and AM (1.48 points) compared to arm M (0.19 points; p<0.001). Of those patients whom were anxious at baseline (HAD anxiety ≥7), 78% of arm AM, 52% of arm A and 36% of arm M achieved a 1.5 point improvement in VAS relaxation (chi-squared p=0.002). At 7 days, the Lar anxiety score
improved in arm A (1.5 points), arm M (1.2 points) with no change in arm M (0 points, p=0.003). Conclusion: Acupuncture has an anxiolytic effect seen on two scoring systems in this trial. Further research in this area is warranted.

Keywords: acupuncture, lung cancer, Mesothelioma, Anxiety

POSTER SESSION 3 – P3.05: PALLIATIVE CARE/ETHICS SYMPTOMS, THERAPEUTIC INTERVENTIONS – WEDNESDAY, DECEMBER 7, 2016

P3.05-007 PROSPECTIVE EVALUATION FOR COMBINATION ANTIEMETIC THERAPY ON CINV IN NSCLC RECEIVING CARBOPLATIN-BASED CHEMOTHERAPY OF MEC

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Background: The incidence of delayed chemotherapy-induced nausea and vomiting (CINV) for non-small cell lung cancer (NSCLC) patients receiving carboplatin (CBDCA)-based chemotherapy (CBDCA+pemetrexed (PEM)/CBDCA+paclitaxel (PTX)) has not been clearly controlled. Methods: We used the combined data from the two prospective observational studies: A nationwide survey of CINV study group and the other prospective observational study in Japan. We assessed whether delayed CINV were controlled with combination antiemetic treatment. We also evaluate risk factors by logistic regression analysis. Results: A total of 240 patients were evaluable in this study. The median age was 66 (range: 34-82) with 173 males and 67 females. Three antiemetics were used in 54 (22.5%) patients. Delayed nausea and vomiting were experienced more commonly in women than in men. Delayed nausea was well controlled with 3 antiemetics than with 2 antiemetics for overall (11.1% vs. 23.1%; P=0.056). Delayed vomiting was well controlled with 3 antiemetics than with 2 antiemetics for women (45.0% vs. 72.3%; P=0.056)). Delayed vomiting was well controlled with 3 antiemetics than with 2 antiemetics for overall (11.1% vs. 23.1%; P=0.057) and for women (20.0% vs. 44.7%; P=0.0962). We identified several risk factors; women (OR=2.903; 95% confidence interval [CI], 1.607-5.242; P=0.0004) and age (OR=1.968; 95%CI, 1.938-9.99; P=0.0142) for delayed nausea, and women (OR=4.252; 95%CI, 2.154-8.394; P=0.0001) and 2 antiemetics (OR=3.140; 95%CI, 1.205-8.179; P=0.0192) for delayed vomiting. Conclusion: Three antiemetics combination are encouraged for NSCLC patients treated with CBDCA-based chemotherapy to alleviate delayed nausea and vomiting.

Keywords: chemotherapy-induced nausea and vomiting, non-small cell lung cancer, carboplatin-based chemotherapy

POSTER SESSION 3 – P3.05: PALLIATIVE CARE/ETHICS SYMPTOMS, THERAPEUTIC INTERVENTIONS – WEDNESDAY, DECEMBER 7, 2016

P3.05-008 MINDFULNESS-BASED STRESS REDUCTION ADDED TO CARE AS USUAL FOR LUNG CANCER PATIENTS AND THEIR PARTNERS: A RANDOMIZED CONTROLLED TRIAL

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Background: Lung cancer patients and their partners report among the highest distress rates of all cancer patients. Possibly because of the poor prognosis and fast deterioration of physical health, limited research has been conducted in lung cancer on how to reduce patients’ and partners’ distress levels. The present study examined the effectiveness of additional Mindfulness-Based Stress Reduction (CAU+MBSR) versus solely care as usual (CAU) to reduce psychological distress in lung cancer patients and partners. Methods: We performed a multicentre, parallel-group, randomized controlled trial (ClinicalTrials.gov: NCT01494883). Patients with lung cancer and their partners were randomly allocated to CAU+MBSR or CAU. MBSR is an 8-week group-based intervention, including mindfulness practice and psycho-education on stress. CAU included anti-cancer treatment, medical consultations and supportive care. The primary outcome was psychological distress. Secondary outcomes included quality of life, caregiver burden, relationship satisfaction, mindfulness skills, self-compassion, rumination and post-traumatic stress symptoms. Outcomes were assessed at baseline, post-intervention and at 3-month follow-up. Linear mixed modeling was conducted on an intention-to-treat sample. Moderation analyses were performed. Results: 31 patients and 21 partners were randomized to CAU+MBSR and 32 patients and 23 partners to CAU. CAU+MBSR patients reported significantly less psychological distress (p=0.010, d=0.69) than CAU patients. Baseline distress levels moderated outcome: those with more distress benefited most from MBSR. Additionally, CAU+MBSR patients showed more improvements in quality of life (p=0.044, d=0.62), mindfulness skills (p=0.005, d=0.76), self-compassion (p=0.017, d=0.75) and rumination (p=0.015, d=0.70) than CAU patients. In partners, no differences were found between groups. Conclusion: Our findings suggest that psychological distress in lung cancer patients can be effectively treated with MBSR. No effect was found in partners. More research is needed on facilitators and barriers of participation to make effective psychosocial interventions more accessible to lung cancer patients and their partners.

Keywords: psychological distress, mindfulness-based stress reduction, randomized controlled trial, lung cancer

POSTER SESSION 3 – P3.05: PALLIATIVE CARE/ETHICS SYMPTOMS, THERAPEUTIC INTERVENTIONS – WEDNESDAY, DECEMBER 7, 2016

P3.05-009 MEDICAL MARIJUANA AND LUNG CANCER: PATIENTS' KNOWLEDGE AND ATTITUDE TOWARDS ITS USE

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Background: Management of cancer-related symptoms in patients with lung cancer can be challenging. Increasing number of patients have turned to cannabis plant to alleviate those symptoms. Some studies have shown potential benefits, however it is still classified as an illegal schedule I drug in the US. There is a shortage of research on its use in cancer patients. Additionally, there is fear, bias and stigma associated with its use. In this study, we set out to investigate patients’ knowledge and views on the use of marijuana. Methods: Patients with advanced lung cancer, over 18 years of age were included. They had to be receiving systemic intravenous treatment (chemotherapy, immunotherapy, biologic therapy), able to give informed consent and fluent in English. Study was explained by a trained research staff, written informed consent was obtained, and patients were given the survey to fill without assistance. Study was IRB approved. Results: A total of 20 patients were enrolled. They were 70% females, 30% males, 15% Hispanic, 5% Asian, 70% white, and 30% black. The majority of patients were symptomatic with 50% having pain, 25% nausea, 30% weight loss, 45% poor appetite and 60% with other symptoms more commonly fatigue. The majority (80%) has heard of the use of medical marijuana for cancer, 40% thought it helped treat the cancer, 75% thought it reduced side effects of treatment, 70% helped with pain, 60% helped with weight gain, and 70% helped with psychological distress. In this group, 82% have considered using marijuana, 70% thought they are able to obtain it. Only 15% said they would smoke it, while 30% would use a vaporized form, and 75% would use it in an edible form. Forty one percent of the patients expressed concerns regarding the legal risk of purchasing marijuana in Florida, while only 23% expressed concerns regarding the legal risk of using it. One hundred percent of the patients felt it should belegal for cancer patients, and 100% expressed the need for a trusted educational resource for learning about Marijuana use. Overall, 94% of the patients would consider using it if legalized. Conclusion: To our knowledge, this is the first study focusing on lung cancer patients and their awareness thereof. More research focusing on this modality for palliation of symptoms in lung cancer patients is urgently needed.

Keywords: Medical Marijuana, palliative care, Cannabis, lung cancer

POSTER SESSION 3 – P3.05: PALLIATIVE CARE/ETHICS QUALITY OF LIFE, Others – WEDNESDAY, DECEMBER 7, 2016
P3.05-010 DEVELOPING TOOLS FOR A SUCCESSFUL THORACIC RAPID TISSUE DONATION PROGRAM

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Background: Advances in cancer treatment have been made through the use of human tumor tissues from patients with refractory disease. Rapid Tissue Donation (RTD) provides an opportunity to gain insight into treatment-resistant cancer by restarting tissue from major tumors and metastasis within 24 hours following a patient's death. The discussion of participation is a delicate process that must consider inherent communication challenges. Prospective patients may perceive their physician’s recruitment efforts for RTD as a sign of loss of hope. Companions may be distressed by the offer. This study examined the decision making of participating in a RTD program for patients with advanced stage lung cancer and their companion. Methods: After a physician-guided introduction of the RTD program, participants with stage 4 lung cancer (n=9) and their companions (n=8) were consented to participate in a qualitative, semi-structured interview assessing their decision-making process and barriers and benefits of enrolling in the program, perceptions of the RTD brochures and satisfaction with the recruitment process. Companions participated in independent and joint interviews assessing their perceptions of patients’ decision to enroll in the program. Coders reviewed the verbatim transcripts of the interviews and applied qualitative thematic analysis to identify emergent themes. Results: The majority of patients chose to enroll in the RTD program as an opportunity to give back to science and upon learning organ donation was not an option for them. All patients had good relationships with their physician and this was a deciding factor for participation. Patients had limited concerns about participation and wanted to be sure their loved ones were not burdened by the process. Companions had more concerns about logistics but all supported patients’ decisions. All participants were comfortable with the recruiting process and their physician’s initiation and subsequent discussion of the program. Some patients indicated that they did not plan to inform extended family members. Two companions reported feeling distressed during a clinical discussion concerning the patients’ participation. Patients and their companions approved of the brochure’s content, including References to death, but often objected to the use of language depicting cancer as a “study” or “fight.” Conclusion: Implementation of an RTD program requires monitoring of the complex communication processes that occur at both interpersonal and institutional levels. Additional research during the ongoing accrual process will continue to assess physician perspectives and seek methods honoring the wishes of patients and companions. R21 CA19432-01 (NCI).

Keywords: Rapid Tissue Donation, Ethics, lung cancer

P3.05-012 ASSESSMENT OF THE IMPACT OF PALLIATIVE CARE ON THE QUALITY OF LIFE IN ADVANCED NON-SMALL CELL LUNG CANCER PATIENTS - A LONGITUDINAL STUDY

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Background: During the last two decades, health-related quality of life (QoL) measurements have been an important issue in understanding the difficulties perceived in many diseases. It is important to assess the health-related quality of life of the patients to know the extent of diseases and conditions affecting individuals general well-being. Studies have shown the effect various determinants of Quality of Life (QoL) in lung cancer patients. This study was done to assess the QoL in individuals with non-small cell lung cancer undergoing palliative care. Methods: Data on QoL were collected using a modified MOS-SF-36 form. A modified version was done in 27 individuals before and after providing supportive or palliative care. A random mixed linear model was used to assess impact of palliative care on Quality of Life with Physical Health Summary score and Mental Health Summary score as main outcomes. All the possible confounding factors were controlled in the study. Results: When values were compared before and after giving palliative care the Physical Health Summary score decreased considerably. (diff=-2.12; 95% CI: [1.40, -0.83]) with small to medium effect sizes. The PHS Score remained lower after being on palliative care for more than 2 years (diff=-5.86; 95% CI: [7.89, -3.63]). J. The Mental Health summary score did not change significantly after giving palliative care (diff=-5.86; 95% CI: [7.89, -3.63]). The Mental Health summary score was higher after HAART for more than 5 years when compared prior to infection. Conclusion: Quality of life is an important determinant in the course of lung cancer. Palliative or supportive care can play a vital role in improving the quality of life in patients with lung cancer.

Keywords: supportive care, Lung Health, quality of life, Cancer

POSTER SESSION 3 - P3.05: PALLIATIVE CARE/ETHICS QUALITY OF LIFE, OTHERS - WEDNESDAY, DECEMBER 7, 2016

P3.05-011 IMPORTANCE OF ASSESSMENT OF MALNUTRITION RISK IN LUNG CANCER PATIENTS

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Background: Malnutrition and cachexia are commonly seen in cancer patients. The aim of this research was to assess overall risk of malnutrition in lung cancer patients. Methods: This prospective observational study that included hospitalized lung cancer patients was conducted in the Institute for pulmonary diseases of Voyvodina, Serbia. International questionnaire for nutrition screening was used for clinical assessment of malnutrition. Subjects were included in this study regardless of lung cancer type, stage of disease and therapy regimen. Results: Out of total 188 patients included, 76.7% were male and 23.3% female. Majority of patients were in ECOG performance status (PS) 1 (74.5%) with diagnosed lung cancer in stages III and IV (39.9% and 42.6% respectively). Most common lung cancer type was adenocarcinoma (50.0%) followed by squamous (35.6%), small-cell (10.6) and other histologic types (3.7%). Majority of patients had Body Mass Index (BMI) ≥20 (87.8%). BMI<18 was observed in 7.4% of patients. Unplanned weight loss in past 3-6 months for more than 10% was present in 16.5% of patients. In this group of patients 20.7% were with high risk, 12.8% with medium risk and 66.5% with low risk of malnutrition. High risk of malnutrition was more frequent in stages III and IV of lung cancer (24.0% and 22.5% respectively) than in stages I and II (13.3% and 5.6% respectively). We observed statistically significant correlation between ECOG PS and risk of malnutrition (p=0.001; r=0.20). Patients with ECOG PS 0 are ten times less likely to have high risk of malnutrition than patients with poorer ECOG PS. Conclusion: This study showed that a significant percentage of lung cancer patient have a high risk of malnutrition therefore it would be advisable to routinely evaluate nutritional status of lung cancer patients regardless of stages and duration of disease.

Keywords: malnutrition, palliative medicine, lung cancer

POSTER SESSION 3 - P3.05: PALLIATIVE CARE/ETHICS QUALITY OF LIFE, OTHERS - WEDNESDAY, DECEMBER 7, 2016

P3.05-013 DEVELOPMENT OF THE KENTUCKY LEADS COLLABORATIVE LUNG CANCER SURVIVORSHIP CARE PROGRAM

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Background: Individuals diagnosed with lung cancer commonly suffer many threats to preserving quality of life, including substantial symptom burden, clinically significant distress, limited social and economic resources, and considerable stigma/bias. Despite these notable challenges, relatively little clinical research is dedicated to developing, evaluating, and disseminating survivorship interventions that address the diverse needs of lung cancer survivors and their caregivers. Methods: To expand and enhance lung cancer survivorship care, the investigative team developed a targeted and tailored psychosocial intervention to address the diverse needs of lung cancer survivors and the challenges faced by their caregivers. Principles of motivational interviewing and shared decision making guided the design of the Kentucky LEADS Collaborative Lung Cancer Survivorship Care program, a flexible and scalable survivorship intervention. Results: Selection of
**P3.05-014 EVALUATION OF HYPONATRAEMIA IN LUNG CANCER PATIENTS: A U.K. TEACHING HOSPITAL EXPERIENCE**

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Background: Hyponatraemia, defined as a serum Na of <135mEq/L, is the commonest electrolyte abnormality in oncology practice. Among cancer patients, it occurs most frequently in small cell lung cancer (SCLC) and is due to inappropriate antidiuretic hormone secretion (SIADH), a paraneoplastic syndrome. The incidence of SIADH in SCLC is 11-15%. We describe the demographics, oncological management and response of hyponatraemia to oncological treatment modalities in hospitalised patients with lung cancer in a large inner-city teaching hospital. Methods: We retrospectively analysed the serum sodium levels in all lung cancer patients admitted to a teaching hospital in the West Midlands between 2007-2013. Data was collected on baseline demographics, histology, tumour stage and grade of hyponatraemia. Mild hyponatraemia was defined as a serum sodium between 130-135mEq/L, moderate between 125-129mEq/L, and severe as <124mEq/L. Results: 182 (108 male; 74 female) patients with lung cancer and documented hyponatraemia were hospitalised between 2007-2013. Median age of patients was 69.2 years (range 33-92 years). 119(65%) had mild, 58(32%) moderate and 5(3%) severe hyponatraemia. 74(40%) were adenocarcinomas, 58(32%) squamous carcinomas, 49(24%) SCLC and 7(4%) had unspecified normal small cell lung cancer. 89(49%) had metastatic disease at diagnosis. 18/42 (43%) small cell, 14/58 (25%) squamous, 23/74 (31%) adenocarcinoma patients had moderate to severe hyponatraemia. 132(74%) of this cohort had active oncological treatment: 93(51%) chemotherapy, 25(14%) radiotherapy, 17(9%) surgery whilst 47(26%) had been supportive care. 28(15%) had a biochemical response to treatment, 11(39%) of these patients were adrenocarcinomas, 10(36%) squamous carcinomas and 7(25%) SCLC. Conclusion: Hyponatraemia in lung cancer patients is widely distributed in various age groups and histological subtypes. Among those admitted with hyponatraemia, severe cases (<124mEq/L) were rare. Higher rates of SIADH are seen in SCLC than in any other malignancy and our data confirmed that, proportionately, more SCLC patients had moderate - severe hyponatraemia than non small cell lung cancer patients. Hyponatraemia does respond to active oncological treatment including chemotherapy, radiotherapy and surgery. Although historically, hyponatraemia is considered a poor prognostic marker, this should not preclude active oncological management. Asymptomatic patients with SIADH have been managed initially by fluid restriction but patient compliance is usually poor. Older medications such as demeclocycline, urea and lithium are limited by variable efficacy, poor palatability and/or toxicity, thus underscoring the need for new approaches. Tolvaptan, a new vasopressin receptor antagonist, can improve hyponatraemia due to SIADH. Further studies are needed to evaluate the prognostic value of hyponatraemia and its treatment in cancer patients.

Keywords: hyponatraemia, lung cancer

**P3.05-016 MITOCHONDIAL PATHWAY MEDIATED APOPTOSIS IS INVOLVED IN ERLOTINIB-INDUCED CYTOXICITY IN HEPATIC CELLS**

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Background: For advanced non-small-cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) mutations, EGFR tyrosine kinase inhibitors (TKIs) including erlotinib are indicated for the first-line treatment. Liver injury is one of many limited toxicities of erlotinib and can greatly affect its safety. This study explored the mechanism of erlotinib-induced hepatotoxicity in vitro and provide experimental evidence for screening potential hepatoprotectors. Methods: LO2 cells, human hepatocytes were cultured for investigating mechanism of erlotinib-induced hepatotoxicity in vitro. The cell inhibition rate was detected by sulforhodamine B (SRB) colorimetric assay and IC50 value was calculated. Apoptosis was evaluated by DAPI staining and Annexin V-FITC/PI staining for flow cytometry, moreover, the variation of mitochondrial membrane potential (ΔΨm) was examined using JC-1 staining. The expressions of apoptosis related protein including cleavage of pro-caspase-9, pro-caspase-3 (c-aspase-9, c-aspase-3), Bcl-2 and Bax were detected with western blotting. Results: We found that erlotinib induced dose-dependent cytotoxicity in human LO2 hepatic cells 72 h after treatment. In other experiments, LO2 cells were treated with erlotinib for 48 h and displayed typical features of apoptosis. Erlotinib caused alteration of nucleus morphology such as chromatin condensation and karyopyknosis. It also induced a raise in the fraction of late apoptotic cells and regulation of apoptosis protein expression including activation of c-aspase-3 as well as c-ASP. Furthermore, 48 h exposure to erlotinib disturbed mitochondrial functions by reducing both the ratio of Bcl-2 to Bax proteins and mitochondrial membrane potential. Conclusion: The results of this in vitro study suggested that erlotinib-induced hepatotoxicity may occur through mitochondrial-pathway mediated apoptosis.

Keywords: Hepatotoxicity, Erlotinib, Mitochondrial pathway, apoptosis
Background: The 5-year observed survival rate for a stage IV non-small cell lung cancer patient is less than five percent. Such a small survival rate begs the questions of how these survivors might feel. Many survivors feel a deep-seated sense of guilt; a phenomenon known as survivor guilt. The goal of the present study was to identify the prevalence of survivor guilt among lung cancer patients, while also pinpointing themes among those who are affected. Methods: A questionnaire containing a subset of the published IGQ-67 Interpersonal Guilt Questionnaire was completed via Survey Monkey by 108 respondents. Respondents were also given a definition of survivor guilt with an open-ended question on their feelings toward surviving lung cancer when others did not. Qualitative analysis was conducted on open-ended text responses for respondents with the most measured survivor guilt. After key qualitative themes were established from the initial survey, focus groups were held in survivors who experienced high and low levels of survivor guilt to further explore the themes. Results: This study indicates that a significant amount of survivor guilt is experienced among lung cancer survivors. 55% of respondents identified as having experienced survivor guilt, yet 63.9% of respondents scored above average on the IGQ-67 Survivor Guilt Scale. Qualitative analysis established five recurring themes among 25% of respondents with the highest measured survivor guilt. Targeted focus groups revealed further commonalities among those with high and low levels of measured survivor guilt. Conclusion: This study identifies the prevalence of survivor guilt in lung cancer survivors and shows survivor guilt as a major psychosocial challenge. Further research across all cancer types must be explored in order to develop effective coping mechanisms for sufferers. This study develops the basis for future research directions in creating tools to identify, assess, and treat survivor guilt in survivors of all cancers.

Keywords: survivorship, survivor guilt, psychosocial, patient support

Figure 1. Differences in goal of therapy by prognostic understanding

**Table 1. Results**

<table>
<thead>
<tr>
<th>1. Prognostic Understanding</th>
<th>2. Goal of therapy</th>
<th>3. Information preference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most likely to care</td>
<td>High</td>
<td>Core</td>
</tr>
<tr>
<td>My treatment can cure me</td>
<td>48/146 (33%)</td>
<td>31/146 (21%)</td>
</tr>
<tr>
<td>Don’t know/Can’t choose</td>
<td>8/146 (5%)</td>
<td>2/146 (1%)</td>
</tr>
</tbody>
</table>

**Figure 1. Association between prognostic understanding (degradable versus non-curable) and goal of therapy (y = 0.426)**
Conclusion: Only 45% of patients know their treatment is not curative, although this study shows they should know the palliative intent. Patients with advanced lung cancer who know they cannot be cured, are more aware of the primary goal of a palliative treatment. 57% and 51% wants to have a conversation about ED care and their prognosis.

Keywords: prognostic understanding, Communication, Lung cancer, Early palliative care

P3.05-020 PATIENTS’ PERCEPTION OF RAPID ONSET OPIOIDS

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Background: Patients with lung cancer often complain of pain, and not always controlled by maintenance managements. Rapid onset opioids (ROO) are prescribed for breakthrough pain. Patients in Korea prefer to take medicine orally. We evaluated patients’ preference of transmucosal ROO in patients with lung cancer. Methods: One hundred and seventy seven patients with lung cancer who complained of pain were interviewed and filled in a questionnaire after perception of ROO before and after their use. Results: Ninety three patients (53%) were older than 65 year old. Patients who cannot classify maintenance drugs and ROO were 78(67%) and 35(20%) before and after use of drugs. At the time of breakthrough pain, 66(37%) and 12(2%) tolerated without ROO before and after use of them. Twenty five (14%) and 87(50%) patients were relieved from pain within 10 minutes with oral and transmucosal drugs. Preference of transmucosal drugs were 68(27%) and changed to 89(50%) after use them. Conclusion: Many patients tolerated breakthrough pain without ROO. Preference to transmucosal drugs changed after use of them. Physicians should educate ROO especially in older patients.

Keywords: Rapid onset opioid

P3.06-001 PHASE I/II STUDY TO EVALUATE SAFETY AND EFFICACY DCVAC/ LuCa WITH 1ST LINE CHEMOTHERAPY +/- IMMUNE ENHANCERS VS CHEMOTHERAPY, STAGE IV NSCLC

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Background: Lung cancer (LuCa) has been the most common cancer in the world for several decades and also the most common cause of death from cancer worldwide. Immunotherapy, for induction of tumor cell specific immune responses destroying tumor cells, has emerged as a promising treatment modality in solid malignant tumors. Studies have shown that chemotherapy can be combined with vaccine without impairing the immune response. Methods: 5LUO1 is a randomized, open, parallel-group, multicenter, international phase I/II study to evaluate the efficacy and safety of DCVAC/ LuCa (active cellular immunotherapy based on dendritic cells) added to standard first line chemotherapy with carboplatin and paclitaxel +/- immune enhancers vs. chemotherapy alone in patients with Stage IV NSCLC. The study was initiated in December 2014 and plans to enroll 105 patients at approximately 12 sites in Czech and Slovak Republics. Eligible patients are required to present with metastatic NSCLC defined by histologically or cytologically confirmation and ECOG score 0-1. All patients will receive Standard of Care (SoC) carboplatin and paclitaxel, and will be randomized 1:1:1:1 to DCVAC/LuCa or DCVAC/LuCa + immune enhancers (pegylated IFN-a2b and hydroxychloroquine) or SoC only. Patients will be stratified by histology subtype adenomatous or squamous cell carcinoma and smoking history. The primary objective is to compare efficacy of DCVAC/ LuCa chemotherapy vs. chemotherapy alone in patients with stage IV NSCLC, as measured by progression free survival (PFS). Secondary objectives include assessments of safety, objective response rate (ORR), duration of response (DoR) and overall survival (OS). Exploratory objectives include comparison of changes in immune responses and search for prognostic biomarkers. Clinical trial information: EudraCT number 2014-003084-37. Results: Section is not applicable Conclusion: Section is not applicable.

Keywords: DCVAC/LuCa, Active cellular immunotherapy, dendritic cell vaccine, NSCLC

P3.06-002 ATLANTIS TRIAL: PHASE III STUDY OF PM01183/ DOXORUBICIN VS. CAV OR TOPOTECAN IN SCLC AFTER ONE PLATINUM-CONTAINING LINE

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Background: PM01183 (lurbinectedin) is a new anticancer drug that blocks trans-activated transcription, induces DNA double-strand breaks and modulates the tumor microenvironment. Synergism in combination with doxorubicin with compelling overall response rates (~67%, including approximately 10% complete responses) was reported in a phase I expansion cohort in 21 second-line SCLC patients (pts) (ASCO 2015, abstract 7509). The most common toxicity observed was hematologic. Methods: Multinational, multicenter (>150 sites), open-label, randomized, phase III study of PM01183/ doxorubicin vs. a control arm with investigator choice of either standard CAV or topotecan (1.5 mg/m2, D1-5 q3wk). A total of 600 pts will be randomized (1:1) and stratified according to ECOG performance status (PS), chemotherapy-free interval (CTFI), known CNS involvement, prior PD-1/PD-L1 based immunotherapy and potential investigator’s control preference. Patients with clinical benefit after 10 cycles of doxorubicin containing combination will continue on single agent PM01183 or CV, until PD or unacceptable toxicity. Interim safety analysis will be performed after 150 pts by an independent data monitoring committee. The most relevant inclusion criteria are: pts ≥38 years old; confirmed diagnosis of SCLC (small-cell carcinomas from unknown site are eligible provided ≥50% Ki-67 expression). One prior platinum containing regimen is mandatory (additional immunotherapy is allowed provided that it was not given in combination with C1), PS 0-2 and adequate major organ function, including normal LVEF. KS: ≥30% at baseline. Pts are excluded if pre-treated with PM01183, doxorubicin or topotecan; symptomatic or steroid requiring CNS involvement or any serious medical condition that might preclude safe compliance with study treatment. The primary objective is to determine a difference in progression-free survival by an independent review committee. Secondary endpoints are all survival, survival rates at 12/18/24 months, antitumor response (RECIST v1.1), duration of response, QoL, safety, subgroup analyses and pharmacokinetics (PK) of PM01183/ doxorubicin arm. First patient is planned in JUL2016. Enrollment is expected to be completed by 4Q17. Results: Section not applicable Conclusion: Section not applicable.

Keywords: phase III, Lurbinectedin, SCLC
(RT) plus SABR/SRS following standard chemotherapy in patients with oligometastatic NSCLC and will undertake an early evaluation of feasibility and toxicity. Methods: SARON is a randomised, multicentre, phase III trial for patients with oligometastatic NSCLC (1-3 sites of synchronous metastatic disease). An early feasibility review will take place after 50 randomised patients. Patients requiring both conventional thoracic RT to the primary and SABR to a thoracic metastasis will be included in a sub-study to more thoroughly assess toxicity and planning issues. 340 patients will be recruited from 30 UK sites, to randomise 306 patients (1:1) to receive either platinum doublet chemotherapy alone (control arm) or platinum doublet chemotherapy followed by radical RT/SABR to their primary tumour and then SABR and/or SRS to all other metastatic sites (investigational arm).

Results: The primary endpoint is OS, and the study is powered to detect an improvement in median survival from 9.9 months in the control arm to 14.3 months in the investigational arm (85% power, 5% two-sided alpha). The secondary endpoints include progression free survival, toxicity, local control of primary and metastases, and quality of life. Conclusion: The study will open in Q3 2016 and is supported by Cancer Research UK (C13530/A18015).

Keywords: Stereotactic ablative radiotherapy (SABR), Stereotactic radiosurgery (SRS), Oligometastatic, non-small cell lung cancer (NSCLC)

P3.06-006 ENDPOINTS IN REPORTS ON CLINICAL TRIALS FOR ADVANCED LUNG CANCER

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Background: In reporting experience from clinical trials for advanced lung cancer, proper presentation of endpoints should support decisions for patient management and offer a basis for further research. This postulate was tested in a survey of published trials. Methods: The survey includes reports on trials of systemic treatment of advanced lung cancer published between 2013 and 2015 and included in the PubMed database. After excluding reviews, discussion papers, trials on palliative measures, trials on local treatment, case reports and Phase I clinical trials, 316 reports on a total of 303 trials were identified. Analysis focused on primary and secondary endpoints. Results: The analysis includes 124 single-arm Phase II trials, 170 randomised Phase II or Phase III trials and 9 Phase IV trials, with a total of 75.467 patients. Only 31 reports dealt with small-cell lung cancer. The main treatment modalities were cytotoxic drugs (100 trials), targeted drugs alone or in combination with chemotherapy (168 trials) or immunotherapy (21 trials). Median interval form closure of recruitment to publication was 35 months and exceeded 6 years in reported outcome measures. No short-term outcome measures (such as 30 or 90 day mortality) were reported. Conclusion: This systematic review has highlighted significant variation in practice in outcome measure reporting in studies of radical lung cancer treatments. A large number of different outcome measures were reported, the majority of which were not defined. Where apparently identical outcome measures were reported in more than one study, definitions were inconsistent. Outcome measures relating to short-term survival were not reported at all, despite the fact that long-term survival in this patient population was uncommon. Only one study included patient-reported outcome measures. If lung cancer research is to optimally inform clinical decision making, study endpoints should reflect outcomes that are most meaningful to patients and their clinicians. Variation in outcome-reporting practice, particularly where definitions are lacking and inconsistent, is a significant concern. It threatens the ability of clinicians to assimilate the findings from multiple studies and limits the extent to which the true benefits and burdens of proposed treatments can be understood. Consideration should be given as to whether a core outcome set, incorporating clinically meaningful and patient-reported outcomes, might be warranted in lung cancer. Further research is needed.

Keywords: radical chemotherapy, lung cancer, radical radiotherapy, outcome reporting
Abstracts

P.06-008 EMPLOYING REMOTE WEB CONSENTING AND SOCIAL MEDIA TO FACILITATE ENROLLMENT TO AN INTERNATIONAL TRIAL ON YOUNG LUNG CANCER

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Background: In 2016, the Addario Lung Cancer Medical Institute (ALCF) launched a prospective study to characterize somatic and germline genomics of adolescents and young adult (AYA) patients under the hypothesis that lung cancer diagnosis at younger ages (<40) are more likely to have targetable genomic alterations. It is estimated that less than 2% of those newly diagnosed with lung cancer globally are AYA, thus presenting a striking recruitment challenge. Methods: The study workflow includes a dedicated website enabling e-consenting so patients can participate remotely from anywhere in the world, including the underserved, and employs social media to share our trial. We have an integrated data and bio repository that allows for seamless communication and completion of study activities including routing of blood and tumor specimens. ALCF’s “sister” foundation, the Bonnie J. Addario Lung Cancer Foundation, played a key role in educating patient and caregiver communities, including a social media campaign. Results: Accrual opened July 23, 2014. In the first 5 weeks of the study, 37 subjects consented versus the 5 projected. Of the 37 initially consented, 36 enrolled via the remote web portal. As of June 15 2016, 104 subjects are enrolled (128 consented) in the study from 10 countries following a social media campaign of 89 discrete postings resulting in 21,062 active users out of 391,222 individual viewers and 675,680 impressions. Of the 104 subjects enrolled to date, 49% entered the study via the remote study portal with the balance recruited locally by participating ALCF study sites. 45% of total accruals to date resulted from the education outreach by patient advocacy and patient to patient social networking.

Conclusion: This study clearly demonstrates the utility, speed and feasibility of remote, web-based screening and consenting platforms supported by patient-centric, advocate-driven social media efforts as novel approaches to “bringing research to the patient” for global clinical trials.

Keywords: E-consenting, Global, advocacy

P.06-009 MULTIPLE ORAL PRESENTATIONS AT MAJOR INTERNATIONAL CONFERENCES FROM A SINGLE CLINICAL TRIAL ARE COMMON

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Background: Such presentations at major international conferences can expose oncologists to new and exciting information; however, the costs for both the presenter and the sponsoring institution can be significant. The multiple presentations of a single clinical trial add a further challenge and can be resource limiting. The authors present a single clinical trial that was presented in over 10 oral presentations at major international conferences.

Methods: The study was a prospective, single-arm, open-label phase II trial of pembrolizumab for relapsed/refractory ALC (NCT02245204). The trial was presented at 10 major international conferences over 2 years.

Results: The trial included 36 subjects enrolled at 10 sites. The overall response rate was 47.2% (95% CI: 29.8-63.2). Complete response rate was 3.3% (95% CI: 0.4-15.7). The estimated median PFS in all subjects was 8 months (95% CI: 7.1-11.2). The median OS was 12.4 months (95% CI: 11.6-20.2). The trial data were presented in oral presentations at 10 major international conferences over 2 years. The estimated median OS increased as the proportion of patients who were actually dead but censored in the HD increased. When this proportion was 25%, 50% and 75%, the estimated median OS was 27.8 months, 33.8 months, and 37.2 months for HD-SCLC, respectively, and 12.5 months, 13.1 months, and 13.7 months for ED-SCLC. Obviously, this discrepancy reflects the limitation of HD-based survival analysis since medical records do not trace all patients until death, especially for those who did not return for subsequent follow-up care. Conclusion: Incomplete follow-up, by increasing the number of censoring events, could result in spurious prolongation of overall survival, which warrants caution in interpreting the HD-based survival analysis.

Keywords: medical record, follow-up loss, survival analysis, censoring

Poster Session – P.06: Trial Design/Statistics

OTHERS – WEDNESDAY, DECEMBER 7, 2016

P.06-007 THE CONSEQUENCE OF INCOMPLETE FOLLOW-UP IN HOSPITAL-BASED SURVIVAL STUDY AS COMPARED WITH NATIONAL VITAL STATUS-BASED RESULTS

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Background: Loss to follow-up (FU) is an important issue in survival analysis using the data based on hospital records. To better address the magnitude of this issue in a real clinical setting, we compared survival outcomes from hospital database with those from national cancer registry data which incorporated national vital status record method. From the hospital database of National Cancer Center Hospital, Korea, we identified 970 small cell lung cancer (SCLC) patients who were treated between 04/2001 and 04/2013. Most of them were male (n = 854) and smokers (n = 906). Median age was 63 years (range: 32-80 years). We made two survival datasets, hospital-based dataset (HD) and cancer registry-based dataset (CD). Results: Of 352 LD-SCLC patients, there were 144 deaths in the HD and 107 additional deaths were identified in the CD (Total= 251). There was no difference in median progression-free survival (PFS) between the HD and CD (12.7 months [95% CI, 10.5-14.9] vs. 12.4 months [95% CI, 10.8-14.2]). But, median OS in the HD was significantly longer than in the CD (55.7 months [95% CI, 35.8-115.6] vs. 26.3 months [95% CI, 22.8-30.8]). The 5-year survival rate of LD-SCLC was 48.7% vs. 29.6% in the HD and CD, respectively. For 618 ED-SCLC patients, there were 234 deaths during the 5 years. In HD and CD, there were 241 additional deaths that were confirmed in the CD (Total= 575). Median PFS of the HD was similar to that from the CD (6.5 months [95% CI, 6.2-6.9] vs. 6 months [95% CI, 6.1-6.8]). Median OS of HD was 14.5 months [95% CI, 13.5-16.9] significantly longer than that of CD (11.9 months [95% CI, 11.2-12.9]). The 5-year survival rate of ED-SCLC in the HD and CD was 11.5% and 3.5%, respectively. In the simulation analysis, the estimated median OS increased as the proportion of patients who were actually dead but censored in the HD increased. When this proportion was 25%, 50% and 75%, the estimated median OS was 27.8 months, 33.8 months, and 37.2 months for HD-SCLC, respectively, and 12.5 months, 13.1 months, and 13.7 months for ED-SCLC. Obviously, this discrepancy reflects the limitation of HD-based survival analysis since medical records do not trace all patients until death, especially for those who did not return for subsequent follow-up care. Conclusion: Incomplete follow-up, by increasing the number of censoring events, could result in spurious prolongation of overall survival, which warrants caution in interpreting the HD-based survival analysis.

Keywords:Endpoints in clinical trials; NSCLC; SCLC; Quality of life
Background: Traditionally, study results have been presented as abstracts at major scientific meetings at the conclusion of the analysis. Recently, presentations of studies in progress and updates to previously presented data have been allowed at major meetings. The frequency and implications of a single study being presented multiple times, particularly in high profile oral presentations, have not been fully evaluated. Methods: To identify studies presented multiple times, abstracts from an approximately one year period from international conferences for three major societies dedicated largely or in part to lung cancer research were assessed (ASCOS 2015, World Lung 2015, ESMO 2015 and ASCO 2016). Abstracts were selected in a two-step process. The first step was for subject matter based on keywords: NSCLC, SCLC or immunotherapy. Searches differed slightly based on individual website functionality, with ASCO searched by track, World Lung by session and ESMO by individual abstract. In a second step, abstracts for which clinical outcome data was presented from a trial with an identifiable NCT number were selected. Immunotherapy abstracts that did not include the treatment of NSCLC or SCLC were excluded in the second step. Results: 851 abstracts were identified that were related to NSCLC, SCLC or immunotherapy. Of these, 357 referred to a clinical trial. 110 of 357 (30%) described clinical trials that were presented multiple times (mean 2.75, range 2-7), and in 44 (12%), this occurred at the same conference. 113 of 357 abstracts (31%) were oral presentations. 75 (66%) of the oral presentations presented data from clinical trials that were presented multiple times, including 35 (31%) which were presented as oral presentations at least twice. Of the 16 unique clinical trials leading to multiple oral presentations, a variety of issues led to the duplicate presentations, including different cohorts of the same trial, biomarker analysis, analysis by one study variable, or simply updated data. In total, only 6 of 16 of these studies presented additional patients in a subsequent oral presentation, presenting unique cohorts, and the other four presenting updated data that included additional patients, in one case, fewer than ten patients. Conclusion: There is a pattern of multiple presentations of clinical trials, particularly in oral presentations, at major meetings. Although a second oral presentation of an abstract may sound confirmatory to a conference participant, in most cases, data presented in subsequent oral presentations related entirely to patients whose data was presented in the previous oral presentation. Keywords: clinical trial, lung cancer, Oral presentation, Immunotherapy

P3.07-001 NIVOLUMAB FOR PATIENTS WITH ADVANCED NON-SQUAMOUS NON-SMALL CELL LUNG CANCER: A COST-EFFECTIVENESS ANALYSIS INCLUDING PD-L1 TESTING

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Background: Nivolumab (NIV) is approved in several countries for pre-treated patients with advanced non-small cell lung cancer (NSCLC). UK NICE previously reported that NIV is not cost-effective compared with DOC for the treatment of squamous NSCLC. Here, we report cost-effectiveness for nonsquamous NSCLC, and consequences of patient selection by PD-L1 testing. Methods: Based on the published results of the CheckMate 017 trial (Borghasi et al, NEJM 2015), we performed a literature-based health economic modelling study to estimate the incremental cost-effectiveness ratio (ICER) of NIV versus DOC for the Swiss health care setting. We estimated the probability of reaching cost-effectiveness based on a willingness to pay (WTP) threshold of CHF100,000 per QALY. Results: The base case model, NIV (mean costs CHF 66’668; mean effect 0.69 QALYs) compared to DOC (mean costs CHF 77’860, mean effect 0.53 QALYS) resulted in an ICER of CHF 177’478 per QALY gained. Selecting patients for NIV by PD-L1 testing (threshold ≥1%), resulted in a base case ICER of CHF124’891 per QALY gained, compared to treating all patients with DOC. Reduction of NIV price, dose, or treatment duration, all reduced the ICER partially below an assumed WTP of CHF100’000 per QALY (see Table 1). Cost-effectiveness was strongly influenced by health state utilities. Table 1 Results of the base case and scenario analyses

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Treatment</th>
<th>Cost (mean)</th>
<th>Effect (mean)</th>
<th>Effect QALY (mean)</th>
<th>Cost QALY (mean)</th>
<th>Incremental cost (mean)</th>
<th>Incremental effect</th>
<th>ICER CHF</th>
<th>Incremental effect</th>
<th>ICER CHF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base case</td>
<td>DOC</td>
<td>37’618</td>
<td>10.99</td>
<td>0.53</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NIV</td>
<td>66’208</td>
<td>15.42</td>
<td>0.69</td>
<td>DOC</td>
<td>28’589</td>
<td>0.16</td>
<td>177’478</td>
<td>14.1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PD-L1 ≥1%</td>
<td>74’968</td>
<td>17.26</td>
<td>0.79</td>
<td>35’530</td>
<td>0.27</td>
<td>123’267</td>
<td>19.7%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NIV</td>
<td>6’941</td>
<td>0.11</td>
<td>0.79</td>
<td>DOC</td>
<td>32’274</td>
<td>0.26</td>
<td>124’891</td>
<td>22.1%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

DOC= docetaxel, NIV=Nivolumab, QALY= quality adjusted life years, ICER= incremental cost effectiveness ratio, CHF=Swiss Francs Conclusion: At its current price, NIV is not cost-effective compared with DOC for the treatment of patients with nonsquamous NSCLC. Price reduction and/or patient selection by PD-L1 testing would be highly recommendable from a socio-economic viewpoint.

Keywords: lung cancer, Nivolumab, docetaxel, Health economic analysis
Abstracts

P3.07-003 EFFECTIVENESS OF PEMETREXED IN ADVANCED NON-SQUAMOUS NSCLC AND ESTIMATION OF ITS IMPACT ON PUBLIC HEALTH IN FRANCE

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Background: Changes to national reimbursement criteria in France may limit patient access to pemetrexed. In the absence of head-to-head comparative clinical outcomes, we compared various induction–maintenance (I–M) sequences used in advanced non-squamous (nssq) non-small cell lung cancer (NSCLC) in France. We estimated the impact of not treating with pemetrexed, compared with current French practice, in terms of life-years (LYs) and quality-adjusted life-years (QALYs). Methods: Progression-free survival (PFS) and overall survival (OS) rates for different first-line I–M sequences used in France in clinical practice were assessed following literature review and network meta-analysis using a sequential decision analytic model adapted for the French healthcare setting. LYs and QALYs (using French EQ5D values) were estimated for sequences with and without pemetrexed. Conservative assumptions were made for missing data. First-line treatment pattern data were taken from the overall European FRAME prospective observational study cohort (Moro-Sibilot. Lung Cancer 2015). The target population for first-line pemetrexed therapy was derived from a French National Authority for Health Pemetrexed Assessment Report (HAS 2016). Results: In the base-case, the I–M sequence pemetrexed+cisplatin—pemetrexed was associated with the longest median PFS and OS (5.98 and 12.88 months, respectively) for all comparators when pemetrexed rather than best supportive care was used as maintenance. By weighting treatment sequences by FRAME (LYs) and quality-adjusted life-years (QALYs) were estimated for all sequences. Conclusion: According to the results of this modelled analysis, compared with current French practice, limiting access to pemetrexed for the I–M treatment of patients with advanced nssqNSCLC could result in substantial loss of LYs and QALYs in this population.

Keywords: pemetrexed, effectiveness, advanced non-squamous NSCLC, France
Conclusion: Based on current list prices in Israel, the estimated mid-point for total treatment cost is the 5th cycle for Non-Sq NSCLC and the 4th cycle for Sq NSCLC. Our data may represent a basis for risk sharing discussion between the payers and the manufacturers.

Keywords: Nivolumab, economic model, non-small cell lung cancer (NSCLC), risk sharing

Figure 1 – Time equivalents to a one level decrease in side effects

Figure 1 presents the time equivalents of a one level decrease in side effects. The bars represent the mean time equivalent and the brackets around the bars represent its standard error. The box plots represent the 95% confidence interval (CI) around the mean time equivalent with the whiskers representing the 95% CI and the box representing the 75% CI.

Conclusion: Despite the limitation of this small, retrospective study, the results indicate that avoiding the long-term side effects could be valued even more highly for some respondents. For example, the 95% confidence interval for time equivalence of functional long-term side effects ranged from 0.62 to 13.31 months.

Keywords: patient preference, public health, discrete choice experiment, health policy

Figure 2 – Midpoint of the indifference curves for the collateral damage

Figure 2 shows the midpoint of the indifference curves for the collateral damage associated with life-long side effects. The indifference curves are estimated using their time equivalents by using mixed logit. Using PFS as the numeraire, the preference for long-term side effects was estimated using mixed logit. Using PFS as the numeraire, the preference for long-term side effects was estimated using mixed logit. Using PFS as the numeraire, the preference for long-term side effects was estimated using mixed logit.
(CPU) represent the use of a compound approved by the FDA/EMA-EU before its approval by local regulatory authorities. CPU provides accelerated access to novel compounds to patients otherwise unable to get the treatment.

Methods: This is a retrospective analysis of 102 patients treated with nivolumab, osimertinib, or nintedanib within a CPU in a single tertiary Israeli cancer center. Basic patient demographics, different logistic treatment aspects and the time from FDA/EMA-EU approval to reimbursement approval for these compounds in Israel were analyzed. Results: We started nintedanib program by July 2016 when the official MOH approval was 16 months later in Nov 2015. Osimertinib program was started a year after the official approval by MOH and was approved for reimbursement 4 months prior to drug registration. Nivolumab for Non-squamous was approved 6 months before approval, while for Squamous the label was approved by MOH 2 months after starting the compassionate program. Reimbursement approval was received 6 months thereafter for nivolumab (Squamous NSCLC). Two out of the three drugs in the program were approved for reimbursement, one even before MOH registration. (See Table next page)

| Table 1, Summarizing data for patients enrolled in compassionate programs (Jan 2014 - May 2016) |

<table>
<thead>
<tr>
<th>Age at Time of Diagnoses</th>
<th>Total Patients</th>
<th>Female (%)</th>
<th>Male (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-24 years</td>
<td>42</td>
<td>22 (52%)</td>
<td>20 (48%)</td>
</tr>
<tr>
<td>25-34 years</td>
<td>38</td>
<td>20 (52%)</td>
<td>18 (48%)</td>
</tr>
<tr>
<td>35-44 years</td>
<td>26</td>
<td>13 (50%)</td>
<td>13 (50%)</td>
</tr>
<tr>
<td>45-54 years</td>
<td>24</td>
<td>12 (50%)</td>
<td>12 (50%)</td>
</tr>
<tr>
<td>55-64 years</td>
<td>18</td>
<td>9 (50%)</td>
<td>9 (50%)</td>
</tr>
<tr>
<td>65+ years</td>
<td>11</td>
<td>5 (45%)</td>
<td>6 (55%)</td>
</tr>
</tbody>
</table>

Conclusion: Compassionate use programs allow access to new cancer drugs prior to their approval by the regulatory authorities, increases physicians' experience with novel compounds and may affect reimbursement approval.

Keywords: Compassionate use program, osimertinib, lung cancer, Nivolumab


P3.07-009 USE OF ADJUVANT CHEMOTHERAPY FOR NON-SMALL CELL LUNG CANCER: THE REAL-WORLD CLINICAL PRACTICE IN TAIWAN

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Background: Adjuvant chemotherapy is the standard treatment for selected patients with non-small cell lung cancer (NSCLC) following curative surgery. This study evaluated the use of adjuvant chemotherapy for these cases among the general population in Taiwan. Methods: A population-based cohort was established by searching the database of the Taiwan Cancer Registry System to identify patients newly diagnosed with NSCLC for the period covering 2005 to 2009. Our target was patients with stage I, II and IIIA NSCLC who had undergone curative surgery. Medication prescription data were retrieved from the National Health Insurance Research Database, Taiwan. Chemotherapy administered within 3 months after the surgery was defined as adjuvant chemotherapy. Results: A total of 5789 patients received curative surgery for NSCLC, and the 1277 (22.1%) who had undergone adjuvant chemotherapy were included in this study. Overall, the most common adjuvant chemotherapy regimen was platinum plus gemcitabine (P + G) (25.7%), followed by platinum plus vinorelbine (P + V) (18.4%). For patients with stage II or IIIA disease, P + G remained the most common regimen, respectively (29.0% and 29.0%). However, for patients with stage I disease, the most common regimen was tegafur/uracil (30.7%). Analyzed by the diagnosis year, P + G was the most commonly used adjuvant chemotherapy regimen until overtake by P + V in 2009. Conclusion: Platinum plus gemcitabine regimen was the most commonly used adjuvant chemotherapy regimen in patients with operated stage I and IIIA NSCLC in Taiwan from 2005 to 2009.

Keywords: Gemcitabine, vinorelbine, non-small cell lung cancer, adjuvant chemotherapy


P3.07-010 ECONOMIC EVALUATION OF GEFTINIB VS. ERLOTINIB FOR FIRST LINE IN NSCLC EGFRM UNDER THE PERSPECTIVE OF BRAZILIAN HEALTH SYSTEM

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Background: About 28,220 new cases of lung cancer are going to be diagnosed in Brazil in 2016. The epidemiological growth factor receptor (EGFR) is a transmembrane protein with tyrosine kinase activity associated with growth, survival, proliferation and differentiation in different human cells. Approximately 25.5% of patients with non-small lung cancer cells (NSCLC) in Brazil present activating mutations in EGFR gene, which confers sensitivity to tyrosine kinase inhibitors (gefitinib and erlotinib). Methods: Given the similarity in efficacy observed in RCTs, an economic evaluation under the perspective of the public and private sectors in Brazil was performed using a Markov model. Estimation of direct medical costs was calculated in a group of advanced NSCLC patients with EGFR mutations, undergoing first line treatment with one of the target therapies. A discount rate of 5% was applied on future costs/benefits and the rate of adverse events was extracted from a meta-analysis to estimate its costs. Results: According to the model, patients with locally advanced or metastatic NSCLC who have EGFR activating mutations undergoing treatment firstline with gefitinib required less resource versus erlotinib in both perspectives as shown in Table 1, mainly due to the price difference between the drugs (USD 984.22 versus USD 2,033.15 in the public and USD 1,440.31 versus USD 2,439.78 in the private). Table 1. Estimated total costs for first line treatment with gefitinib or erlotinib

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Treatment Costs (USD)</th>
<th>Incremental Costs (USD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Private Sector</td>
<td>Gefitinib 26,637.12</td>
<td>Erlotinib 42,110.00</td>
</tr>
<tr>
<td>Public Sector</td>
<td>Gefitinib 16,134.00</td>
<td>Erlotinib 32,045.40</td>
</tr>
</tbody>
</table>

Exchange rate USD = 3.30 BRL (July 2016) Regarding costs related only to
the management of adverse events, both strategies were similar in the public perspective (USD 94.15 for gefitinib versus USD 98.21 for erlotinib); however, gefitinib costs were lower than erlotinib (USD 625.27 versus USD 941.32, respectively) in the private sector. Conclusion: First-line treatment with gefitinib was dominant in comparison with erlotinib for NSCLC patients with EGFR mutation in both public and private sectors in Brazil.

Keywords: Erlotinib, NSCLC, gefitinib, economic evaluation

POSTER SESSION 3 – P.07: REGIONAL ASPECTS/HEALTH POLICY/PUBLIC HEALTH

Other – Geographical Differences – WEDNESDAY, DECEMBER 7, 2016

P.07-011 GEOGRAPHICAL VARIATION IN THE USE OF RADIOThERAPY AND SURGICAL RESSECTION FOR TREATMENT OF NON-SMALL CELL LUNG CANCER IN ENGLAND

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Background: Despite global improvements in survival non-small cell lung cancer (NSCLC) remains lethal, with 20% five year survival in a limited number of developed nations. Fit, early stage NSCLC patients can be offered curative treatment, using surgery or radical radiotherapy. Geographical variation in surgery usage in England has previously been demonstrated. We aimed to further investigate this variation, incorporating all curative treatments and considering associated survival methods. Information on 143,886 patients diagnosed with a first NSCLC between April 2005 and December 2013 in England was extracted from the national cancer registration dataset linked to radiotherapy treatment and Hospital Episode Statistics data. In England Clinical Commissioning Groups (CCG) are the statutory bodies responsible for the planning and commissioning of healthcare services for their local area. We calculated the proportion of patients receiving curative treatment in each CCG, and created quintiles from the resulting distribution. Logistic regression was used to assess the effect of age, sex, stage, comorbidity, performance status and socio-economic deprivation on curative treatment usage. Multivariable Cox regression models were used to analyse survival in relation to curative treatment quintile. Results: Overall, 29,580 (20.6%) non-CCG patients underwent resection and 9,403 (6.5%) received radical radiotherapy. The proportion of patients receiving curative treatments ranged from 11.8% to 31.7% across English CCGs and decreased with advancing age (p < 0.001), increasing stage (p < 0.001) and worsening in performance status (p < 0.001). The proportion of patients receiving curative treatment was greater for females compared with males (p < 0.001). The absolute risk of dying within 5 years ranged from 90% in the lowest treatment quintile to 85% in the highest. Increasing curative treatment rates were associated with lower mortality (p < 0.001), with an adjusted HR of 0.93 (95% CI 0.92-0.95) in the highest treatment quintile compared with the lowest. Conclusion: Despite adjustment for case-mix variables we demonstrated that significant variation in the use of curative treatment for NSCLC persists across CCGs with increasing curative treatment rates associated with lower mortality. There is a need to further explore the factors driving this variation in order to guide changes in care which may deliver improved outcomes.

Keywords: non-small cell lung cancer, resection, radical radiotherapy, England

Conclusion: Socioeconomic factors, including lack of insurance, are associated with disparities in use of adjuvant therapy as recommended by National Comprehensive Cancer Network guidelines. These disparities have significant impact on patient outcomes. Future work should focus on improving access to appropriate adjuvant therapies among the uninsured and socioeconomically disadvantaged.

Keywords: lung cancer, guidelines, Adjuvant therapy, disparities

POSTER SESSION 3 – P.07: REGIONAL ASPECTS/HEALTH POLICY/PUBLIC HEALTH

OTHER – GEOGRAPHICAL DIFFERENCES – WEDNESDAY, DECEMBER 7, 2016

P.07-013 DETERMINING EGFR AND ALK STATUS IN A POPULATION-BASED CANCER REGISTRY: A NATURAL LANGUAGE PROCESSING VALIDATION STUDY

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Background: Population-based data on Epidermal Growth Factor Receptor (EGFR) and Anaplastic Lymphoma Kinase (ALK) gene test status can inform about real-world molecular testing practices and their impact on treatment decisions and outcomes. Yet no efficient methods are available for population-based cancer registries to ascertain molecular testing data of non-squamous non-small-cell lung cancer (NS-NSCLC) from electronic pathology (e-path) records. We sought to validate natural language processing (NLP) systems to accurately ascertain EGFR and ALK test use and results in patients with stage IV NS-NSCLC included in the Fred Hutchinson Cancer Research Center’s Cancer Surveillance System (CSS), a part of the U.S. Surveillance, Epidemiology, and End Results (SEER) program. Methods: We identified 4,279 e-path reports available in the CSS corresponding to 1,634 patients diagnosed with stage IV NS-NSCLC between 09/1/2011 and 12/31/2013. Using a random sample of 426 (10%) reports, we developed and trained an NLP system to detect EGFR mutation and ALK gene rearrangement test use (test result reported vs. not reported), and test results (positive vs. negative among reported tests). Two oncologists reviewed all e-path reports
**Abstracts**

and resolved discrepancies by consensus to determine the gold-standard classification of test use and results. We report preliminary estimates of the NLP sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for EGFR and ALK test use based on a second random sample of 426 reports (testing subsample). Results: Of 61,634 patients, mean age was 68 years, 815 (50%) were male, 1424 (87%) were white, and 1,347 (82%) had adenocarcinoma histology. Based on the gold-standard classification, in the training subsample, 126 (30%) and 103 (24%) reports contained information about EGFR and ALK test results, respectively. In the testing subsample, 139 (32%) and 115 (27%) had information about EGFR and ALK test results, respectively. In the testing subsample, the NLP system correctly detected 135 reports that contained EGFR test results and 285 that did not (sensitivity=97%; specificity=99%; PPV=99%; NPV=99%), respectively. The NLP system correctly detected 113 reports that contained ALK test results and 307 that did not (sensitivity=98%; specificity=99%; PPV=97%; NPV=99%), respectively. Conclusion: NLP is a likely valid method for capture of EGFR and ALK test use from e-path reports. Ongoing analyses include the NLP validity for ascertainment of test results among reported EGFR and ALK tests in this initial dataset and in a separate validation dataset of 3,247 pathology reports, all of which will be reported subsequently.

**Keywords:** molecular testing, Natural Language Processing, Pathology

**Poster Session 3 – P3.07: Regional Aspects/Health Policy/Public Health – Wednesday, December 7, 2016**

**P3.07-015 Patterns and Risk Factors of Patient Flows Across Different Geographic Health Service Units for Lung Cancer Surgery**

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**Background:** To date lobectomy patient flows across different geographic units and time periods has not been quantified; little is known about associations between hospital and patient-level factors and travel choices for surgery and the subsequent outcomes. We explored these issues as well as the robustness of the aforementioned associations with changing geographic health service units. Methods: The New York Statewide Planning and Research Cooperative System database (2007-2012) was used to select lung cancer patients who underwent lobectomy by Video-Assisted Thoracic Surgery (VATS) or open thoracotomy techniques. Hierarchical logistic regressions were used to examine factors associated with surgeries occurred within or outside of patients’ geographic units: Health Service Regions (HSRs), Health Referral Regions (HRRs), and Health Service Areas (HSAs), respectively. Results: A total of 9,655 lobectomies (43% of which were VATS) from 8 HSRs, 21 HRRs, and 145 HSAs were identified. At the state-level, 17%, 22%, and 56% of the lobectomies occurred outside of patients’ HSRs, HRRs, and HSAs, respectively; the percentages varied spatially but the spatial patterns remained stable from 2007 to 2012. Travel-out patients were more likely to be male or with private insurance, and less likely to be non-Hispanics Blacks, Hispanics, or with Medicaid insurance. Travel-out lobectomies were more likely to be performed by VATS, in urban setting, teaching hospitals, with higher lung surgery volume, and higher numbers of surgeons. In-hospital mortality of travel-out lobectomies was not significantly different from that of the stay-ins. These associations were consistent among models using different health service geographic units. Conclusion: Lung cancer patients tended to travel farther to be treated with VATS in urban/teaching hospitals with high surgery volume and surgeon volumes. Other independent determinants of the travel choice included sex, insurance type, and race/ethnicity. Patients’ choices and preferences should be taken into account when planning specialized health care delivery services.

**Keywords:** patient flows, lung cancer, health services, VATS lobectomy

**Poster Session 3 – P3.07: Regional Aspects/Health Policy/Public Health – Wednesday, December 7, 2016**

**P3.07-016 Ontario’s Episode-Based Funding Model Reveals Practice Variations in Adjuvant NSCLC Chemotherapy**

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**Background:** A new episode-based funding model (FM) for ambulatory systemic therapy was implemented in Ontario, Canada in April 2014. The FM bundled reimbursement for components of care, including initial consultation, treatment episodes delivered with adjuvant/curative (AC) or palliative intent and supportive care. Options for evidence-informed AC regimens and their optimal number of treatment cycles and chemotherapy suite visits were informed by the provincial lung Disease Site Group (DSG) based on published literature or group consensus. It was expected that cisplatin-vinorelbine (CISPvinO) would be the most commonly used regimen as CISPvinO was used in the clinical trial conducted in Canada that established CISPvinO was a standard of care and is recommended in Ontario’s adjuvant chemotherapy practice guideline. Methods: The utilization of AC was analyzed for 35 systemic treatment facilities in Ontario comparing actual practice (AP) with “best practice” (BP) (cycle number). For this analysis, cases were included if they started a new course of AC after January 1, 2016 and completed the treatment between July 30, 2015. Results: The percentage of patients with stage II/IIIa NSCLC

**Keywords:** palliative care, Treatment planning, Quality of care, survivorship
receiving AC has been stable at 50–55% for over five years. In this analysis, 1,531 cases received some form of AC. 506 cases received chemotherapy with XRT (usually etoposide-cisplatin) and these cases were assumed to be Pancost tumours or stage IIA disease on neoadjuvant therapy. The most common regimens prescribed without XRT were cisplatin-vinorelbine (CISP/VINO) (331 cases), cisplatin-etoposide (222), carboplatin-etoposide (154) and carboplatin + vinorelbine (74 cases). For all adjuvant chemotherapy excluding XRT (1,025 cases), AP was equal to BP in only 24% of cases, AP:BP in 73% and AP:BP in 4%. For CISP/VINO, AP:BP was achieved in only 36%, AP:BP in 55% and AP:BP in 9%. For the top 5 hospitals by volume administering AC, BP:AP ranged from 8–45%, AP:BP ranged from 41–73%, AP:BP occurred in 20 cases in 3 facilities.

Conclusion: This analysis of first-year funding data provided insights on how adjuvant chemotherapy is administered in Ontario. As expected, CISP/VINO was the most commonly used AC regimen (32%) when AC was used alone. However, etoposide-cisplatin was also commonly used alone and in combination with XRT and carboplatin was frequently substituted. BP is only achieved in the minority of cases and there is wide institutional variance. Reasons for this variation need to be better understood and opportunities identified to drive efficiency and standardization.


P3.07-017 JOINPOINT REGRESSION ANALYSIS OF LUNG CANCER MORTALITY, TURKEY

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Background: It is important to investigate the variation of the deaths due to lung cancer in time. The aim of this study is to investigate the variations in the rate of deaths due to lung cancer in Turkey. Methods: Data on lung cancer mortality during 2009-2014 years were extracted from the Turkish Statistical Institute and Turkey Public Health Agency mortality data based on International Classification of Diseases 10 (ICD-10) codes C32-C34. For each gender, age group-specific and standardised rates were calculated by direct standardization method (using the world standard population). These were expressed as rates/100,000 persons. The temporal trend in lung cancer mortality rates were tested for age, gender and methods using Joinpoint Regression Analysis. In joinpoint regression analysis, the best-fitting points where the rate changes significantly (increase or decrease) are chosen. Each joinpoint indicates a statistically significant change in trend, and annual percentage change (APC) is computed for each of trend by means of generalised lineer models assuming a Poisson distribution. Results: 119.778 deaths due to lung cancer were recorded: 85.50% (n=102409) of the were in men, 14.50% (n=17369) were in women. The mean of crude rate of lung cancer mortality is from 2009(23.77 deaths/100,000) to 2014(26.78 deaths/100,000) 26.19 in 100,000, in men 44.00 in women 7.74. The mean of lung cancer age-specific standardised rates from 2009(69.4 deaths/100,000) to 2014(54.57 deaths/100,000) is 52.50 in 100,000, in men 83.83 and in women 6.22. Lung cancer mortality rates shows a significant increase between 2009-2014. The rates of lung cancer mortality, between 2009-2014 with 4.2% (.95% Confidence Interval: 3.2 to 5.3) showed an important increase annually(p<0.001). During working period, throughout men the variation 4.1% (2.8 to 5.5) in the lung cancer mortality rates were significant(p<0.001). Similar situation was in women with 5.0% (3.7 to 6.4)(p=0.001)The deaths due to lung cancer in young age (under 44 years) in women (5.2%) is more than men (2.9%) (p=0.001). The decrease of -5.4% (1.5 to 5.3) in deaths due to lung cancer seen in young men(under 45 years) within years was not significant(p=0.20). Similarly in women same age the variation 3.7% (2.7 to 4.3) was not significant(p=0.30). The variation in men between the age 65-74 deaths due to lung cancer between 2009 and 2014 was 3.4% was not significant(p=0.10). Unlike in women in this age group with 3.8% increase(2.25.5) showed significant(p<0.001). The increase in deaths due to lung cancer seen in men in 65 years of age and over 4.4%(3.6.5.2) was significant(p=0.001). With the same result in women 2.6% increase(1.1-4) was significant(p=0.001). Conclusion: Even though deaths due to lung cancer non-significant decrease in male, shows significantly increase above 65 years of age. Increase in lung cancer in young women is remarkable.

Keywords: death rate, lung cancer, sex, age groups


P3.07-018 NEW EUROPEAN CLINICAL TRIAL REGULATION: WHAT’S

GOING ON?

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Background: In the last decade Europe has faced a sharp slowdown in Clinical Research (CR) mainly due to European Directive 2001/20/CE application. Consequently the European Commission enacted the EU Regulation 536/2014 (ER) that is expected to become effective only in 2018, due to delays in the portal development. To investigate the new European regulatory knowledge of the Italian professionals, two online surveys, addressed to Clinical Research Coordinators (CRCs) and Clinical Investigators (CIs), were conducted.

Methods: Two anonymous web-based surveys, both consisting of 17 questions, have been used. Results: The 62.5% and 58.3% of the contacted CIs and CRs respectively answered to the survey. 12% of the CIs have a fully knowledge of the incoming ER while many are only partially (64%) or not (24%) informed. 80.4% of CRs demonstrate a complete knowledge and are already trained. Amongst the evaluated topics, the need of a Reporting Member State in the first stage of the evaluation process is considered as positive by 74% of the CIs and almost 90% believe that this procedure will reduce the approval time. With regards to newly imposed transparency standards, 86% of the CIs would welcome the publication of trial results, while 14% believes that this obligation should only apply to profit trials. Overall 70% of CIs state that staff site’s facilities already met all of the ER imposed requirements. The 50% of CIs foresee that the ER will promote independent CR while 42% supposes that it will essentially affect the profit trials. Even though 71.4% of CRs do not have a definite opinion on ER, 85.7% is convinced that it will have a direct impact on their job. Conclusion: The ERs is a turning point for European CR: it is designed to increase the faster protocol approval with positive effects both on timing and overall costs and it will require a rigorous methodology and an increased quality. The surveys highlighted different opinions among CIs and CRs on Italian ability to rise to this challenge: while CIs believe that the centers already met the imposed requirements with only an initial period of transition, CRs are likely to be more critical, hence it is essential for the management of the centers to engage plans to be ready to the ECTR adoption. This process will involve big efforts and resources, but the payback is the opportunity to be on board of innovative treatments for the Italian patients.

Keywords: clinical trial, Oncology, european regulation


P3.07-019 AMDT LUNG, AN IDEAL LUNG CANCER MDT DATABASE

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Background: The role of multidisciplinary teams (MDTs) is central to lung cancer care in Australia with support at policy level and with the development of a nation-wide lung cancer MDT directory from Lung Foundation Australia. In parallel, the importance of accessible, clinically relevant information from routine data collection in lung cancer (as well as other tumour streams) is receiving increased recognition. National Cancer Institute central hubs for the co-ordination of lung cancer care and therefore have the opportunity to focus on quality assurance as well as analyses of patterns of care and identification and targeting of evidence-practice gaps. MDT meetings can act as central sources of data collection and analysis and as such a standardized approach to lung cancer MDT data collection in Australia is warranted. This study will present the results of a modified Delphi study, surveying Australian lung cancer clinicians, aiming to finalize an ideal clinical dataset for collection through lung cancer MDT multidisciplinary sessions. Methods: A 17-item survey has been circulated to a broad, representative sample of lung cancer clinicians, medical and allied health, in Australia. Clinicians were identified and contacted either as (1) part of a purposive sample or (2) through MDT lead clinicians identified through convenience or through the Lung Foundation Australia Lung Cancer MDT registry. Results of an initial survey will be analyzed and a second-round survey will be circulated to an expert panel drawn from the first-round participants prior to
finalization of the dataset. Results: The first round of the survey is reaching completion at the time of abstract submission. A total of 98 responses have been received across the two sampling strategies in the 4 weeks since surveys were distributed. Initial data analysis showed a predominance of pulmonary physicians, attendance at MDT weekly more than fortnightly, support for inclusion of most of the variables presented in the survey and a leaning towards MDT presentation of complex/multimodality therapy and stage II/IIIa cases rather than all cases of lung cancer. Conclusion: The findings of the study will support the development of a standard dataset for collection at lung cancer MDT meetings. This dataset will be utilized in future planned studies across multiple sites for targeted data intervention and feedback strategies and analysis of effect on lung cancer outcomes.

Keywords: data quality, Multidisciplinary team, lung cancer


P3.07-020 IMPLEMENTATION OF AN INTERNATIONAL VALUE-BASED STANDARD SET OF OUTCOMES FOR LUNG CANCER PATIENTS IN A BRAZILIAN CENTER
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Background: Measurement of value is increasingly important in cancer care, specially in lower-income countries. Grupo COI is a Brazilian private cancer care institution, member of the ICHOM (International Consortium for Health Outcomes Measurement) working group for lung cancer standard set definition. We report here feasibility and results for the first year of implementation. Methods: Lung cancer (LC) patients inclusion started on June/2015. Data were prospectively obtained from medical charts and patients interviews. All patients signed an informed consent (IC) and were only included if they would receive entire treatment at our center. ICHOM standard set outcomes included survival, complications during or within six months of treatment, baseline demographic, clinical, and tumor information and patient-reported quality of life evaluation (EORTC QLQ-C30 and QLQ-LC13). Results: A total of 392 LC patients were admitted at COI, but only 120 patients (30.6%) met inclusion criteria. Main reasons for exclusion were partial cycle of care at COI (64.9%) and any treatment started before IC signature (11.3%). Median follow up was 7.9 months and baseline clinical data are presented in Table 1. Patient reported outcomes (PROs) were obtained from paper and phone calls. PROs assessment deviations were reported in 49 patients (38.5%) and reasons for them were application date error (63.2%) from paper and phone calls. PROs assessment deviations were reported in 49 patients (38.5%) and reasons for them were application date error (63.2%) from paper and phone calls. Median age years (variation) 68 (36 – 91)

Gender
Male 57 (47%)
Female 63 (52%)

Educational Level
Primary 21 (17%)
Secondary 36 (30%)
Tertiary 63 (52%)

Performance status
0-1 101 (84%)
2 6 (5%)
3-4 0
Non specified 13 (10%)

Histology
Adenocarcinoma 66 (55%)
Squamous-cell carcinoma 29 (24%)
Small cell carcinoma 12 (10%)
Others 13 (10%)

Stage
I-II 21 (17%)
III 29 (24%)
IV 70 (58%)

Conclusion: Applying an international value-based outcome standard set at a Brazilian institution is feasible. Based on these first data, improvements on PROs assessment methodology are being considered, like self-report electronic forms. Some inclusion criteria should also be revised to avoid this large number of patients exclusion, in order to reproduce a real-world scenario.

Keywords: lung cancer, value, quality of life


P3.07-021 PREVALENCE OF EGFR MUTATIONS IN BRAZILIAN PATIENTS WITH ADVANCED NON-SQUAMOUS NON-SMALL CELL LUNG CANCER
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Background: Non-small cell lung cancer (NSCLC) accounts for approximately 85% of primary lung cancers, the majority of patients presenting with advanced disease at diagnosis. In the last decades there has been significant progress in the understanding of lung cancer molecular biology, which has influenced on treatment choices. The prevalence of EGFR mutations in non-squamous NSCLC population range from 15% to 40%, depending on the population that has been assessed. Brazilian people are marked by high miscegenation, and there is lack of data about EGFR mutations in this population. This study intends to report the prevalence of such mutations in Brazil. Methods: We performed an observational retrospective study of 324 patients treated for advanced NSCLC from January 2014 to May 2016 from two institutions. 80 (24.7%) patients had squamous NSCLC and were not tested for EGFR mutations. The others 244 non-squamous NSCLC patients had their medical record reviewed and information regards the EGFR mutation status were obtained. Patients were stratified by sex, age, histological subtype, and type of mutation. Results: 51 cases (22% of adenocarcinomas) with EGFR mutations were identified. The most frequent genetic alteration detected was exon 19 deletion (64.7%), followed by L858R mutation (19.6%). 34 EGFR mutated patients (66.7%) were women, as man accounted for 60% of all the NSCLC cases. Conclusion: Our findings support previous studies that showed an EGFR mutation rate about 20% in non-squamous NSCLC and its higher prevalence in women population. This research is also important in terms of public health, since knowing how many cases of mutated NSCLC are expected in this region, better we can manage the costs of these patients treatments.

Keywords: non-small cell lung cancer (NSCLC), EGFR, mutation, Brazil


P3.07-022 PROGRESS AGAINST NON-SMAL-L CELL LUNG CANCER (NSCLC) COMPARED TO OTHER SOLID TUMORS
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Background: The recent genomics revolution has provided unprecedented insights into the molecular complexity of cancer cells. Even within the same individual, tumor cells adapt to their environment, evade treatment attempts, and develop resistance against initially efficacious treatments. NSCLC has been shown to be among the most complex cancer types. Multiple approaches, in combination, hold promise to gain ground against this hard-to-treat disease. At the same time, successful preventative effects can substantially reduce disease burden by decreasing the incidence of the disease. Depending on an individual’s preferences, treatment goals may vary from emphasis of quality of life to seeking a lasting cure even at the cost of substantial side effects. This complex picture of etiology, treatment strategies, and patient preferences must be reflected in any assessment of progress against the disease. Methods: We previously introduced the PACE Continuous Innovation Indicators™ (PACE CII) to measure progress against 12 different solid tumor types (https://pacenetworkusa.com/continuoussinnovation). In the present work, we expanded the functionality of the tool to include an interactive user interface based on the Shiny (R
online) platform that allows for custom-weighted analyses. We used this tool to compare progress against NSCLC with other tumor types when different weights are assigned to different treatment contexts and goals. Results: When assigning the largest weights to advanced and/or metastatic disease, NSCLC has seen the most progress (i.e., E-Score increase) over the past 30 years among the 12 common tumor types included in the tool. When focusing on progress against early stage disease and in the adjuvant context, however, NSCLC loses its top position to breast cancer. In both analyses, evidence for treatments that increase survival begins to accumulate in the 1990s and accelerates in the early 2000s, partly driven by the advent of targeted treatments. Conclusion: The global fight against cancer is a very substantial societal investment, and being able to track progress in specific domains will likely be critical for focusing this endeavor. To account for the complexity of the disease, progress cannot be summarized by a single metric. We here show how the PACE CII can help obtain a multi-faceted, complex picture of progress across the entire spectrum of tumor complexity and based on varying patient values. We encourage the field to use this public database to conduct additional analyses based on individual interests and preferences.

Keywords: evidence, progress, NSCLC, innovation
Abstracts

PUB001 ADVANCED NSCLC PATIENTS AT THE EXTREMES OF AGE IN THE ERA OF EGFR-TKIS

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Background: The clinical characteristics and survival of very young (<40 years) and very old (>80 years) patients with advanced non-small cell lung cancer (NSCLC) are distinct. However, the benefits of epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKIs) to patients at the extremes of age with NSCLC harboring EGFR mutation have not been well studied. We retrospectively studied the effect of extreme age on patients’ clinical characteristics and prognosis. Methods: Of 1510 lung cancer patients diagnosed between November 2010 and March 2014, 555 patients who were tested for EGFR mutations were included. Patients were divided into the following groups according to age: young (<40 years), lower medium (41–60 years), higher medium (61–80 years), and very old (>80 years). Results: Of the 555 patients, 20% (36%) patients were aged ≤40 years and 60 (10.8%) patients were aged >80 years. Young NSCLC patients had a lower BMI (p = 0.003), more brain (p = 0.016) and bone metastases (p = 0.002). Very young lung cancer patients still have poor prognosis even they were EGFR mutant. (EGFR mutation vs. wild type patients, OS: 12 vs. 7.3 months, p = 0.215) Very old NSCLC patients had a lower BMI (p = 0.003) and poor ECOG PS (p = 0.028). Positive EGFR mutation test reverses poor prognosis of elderly NSCLC patients. (EGFR mutant vs. wild type patients, OS: 13.2 vs. 4.9 months, p = 0.003)

Conclusion: We observed EGFR mutations reverse the poor prognosis of old patients with NSCLC. However, young patients with lung cancer have a poor prognosis even if they harbor EGFR mutations.

Keywords: Extreme age, non-small cell lung cancer, Tyrosine kinase inhibitors

PUB002 PREDICTORS OF INCOMPLETE RESECTION IN PATIENTS UNDERGOING ESOPHAGECTOMY FOR CANCER: INDUCTION CHEMOTHERAPY DOES NOT INCREASE R0 RESECTION RATE

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Background: In Patients undergoing esophagectomy for cancer, patients who had an incomplete resection have significantly worse outcome compared to those who had R0 resection. The objective of this study was to determine the clinical factors that predict incomplete resection for patients undergoing esophagectomy for cancer. Methods: A prospective esophageal cancer database was retrospectively analyzed for patients who underwent esophagectomy for cancer over 22-year period. Medical records were reviewed and overall survival was analyzed by Kaplan-Meier method. Univariate and multivariate logistic regression were performed to determine predictors of incomplete resection. Results: Univariate predictors with p-value less than 0.2 were selected for inclusion in the multivariate model. Results: We identified 561 patients who had esophagectomy for cancer. Median age was 64 years (57-72), and 79% were males. Un-bloc esophagectomy were done in 70% of patients. Histology was adenocarcinoma in 72% and squamous cell carcinoma in 28%. Thirty six patients (6%) had an incomplete resection. Median follow up was 59 months. The 3 and 5-year overall survival were 53% and 44% for patients who had R0 resections, compared to 9% and 3% in those who R1 and R2 resection (P<0.001). Multivariate analysis showed that advanced clinical T stage (T3/T4), non-en bloc surgical approach and upper third location were significant predictors for incomplete resection. Preoperative use of induction therapy (chemotherapy or chemoradiotherapy) was not a significant factor. Conclusion: Overall survival following incomplete resection for esophageal cancer is poor. Locally advanced clinical tumor stage, non-en bloc resection and upper third tumors are significant predictors for incomplete resection. Interesting, preoperative use of induction therapies was not a significant factor. Other than careful patient selection, en-bloc resection of esophageal cancer may be the preferred surgical approach in minimizing the risk of incomplete resection.

Table: Univariate and Multivariate Predictors for incomplete resection rates (n=561 patients)

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Univariate Odds Ratio</th>
<th>p-value</th>
<th>Multivariate Odds Ratio</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical stage</td>
<td>2.15 (1.27-3.65)</td>
<td>0.004</td>
<td>2.16 (1.11-4.64)</td>
<td>0.024</td>
</tr>
<tr>
<td>Sex</td>
<td>1.49 (1.05-2.11)</td>
<td>0.022</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>1.03 (1.01-1.06)</td>
<td>0.002</td>
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<tr>
<td>Race</td>
<td>1.40 (0.88-2.38)</td>
<td>0.165</td>
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</tr>
<tr>
<td>History of smoking</td>
<td>1.95 (1.28-3.22)</td>
<td>0.002</td>
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<td></td>
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<tr>
<td>History of alcohol use</td>
<td>1.71 (1.37-2.15)</td>
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<tr>
<td>History of diabetes</td>
<td>2.21 (1.47-3.33)</td>
<td>0.001</td>
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</tr>
<tr>
<td>History of COPD</td>
<td>1.57 (1.16-2.15)</td>
<td>0.005</td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of COPD</td>
<td>1.57 (1.16-2.15)</td>
<td>0.005</td>
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</table>

Keywords: incomplete resection, Esophagectomy, esophageal cancer

PUB003 PREDICTORS OF MORTALITY, MORBIDITY AND PROLONGED LENGTH OF STAY AFTER LOBECTOMY: A POPULATION BASED ANALYSIS

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Background: There is a wide variation in healthcare delivery in the United States. Some of the variation may be due to disparities in the health and socioeconomic status of patients. To evaluate the impact of health and socioeconomic status on outcomes after lobectomy, we sought to evaluate predictors of mortality, morbidity and prolonged length of stay (LOS) for patients undergoing lobectomy in the contemporary era using the Nationwide Inpatient Sample (NIS) database. Methods: We examined all patients >18yr who underwent a lobectomy in the NIS database (2007-2011). Multiple regression analysis was used to evaluate the predictors of mortality, morbidity and prolonged LOS. Results: 165,819 patients underwent lobectomy (2007-2011). Median age 67y, Females 52%. Leading comorbidities were hypertension (HTN, 50.1%), chronic pulmonary disease (CPD, 39.4%), coronary artery disease (CAD,19.0%), peripheral vascular disease (PVD,7.2%), and chronic renal disease (CRD, 4.3%). 60% of lobectomies were performed in teaching hospital setting, and VATS-lobectomy accounted for 26.1% of resections. Overall mortality was 2.2% with a median hospital LOS of 6 days. Intraoperative bleeding occurred in 1.5% of patients. Overall inpatient mortality was 3.6% and mortality increased with advancing age, male gender, congestive heart failure (CHF), thoracotomy approach and low socioeconomic status. Predictors of increased mortality were advancing age, male gender, congestive heart failure, chronic pulmonary disease, chronic renal disease, teaching hospital setting and thoracotomy approach. All of these factors significantly contributed to prolonged LOS as well. Conclusion: For patients undergoing lobectomy in the United States, health and socioeconomic factors of patients together with healthcare delivery methods significantly predict mortality, morbidity and prolonged LOS. Preoperative risk modification, careful patient selection and appropriate use of VATS approach may serve to improve perioperative outcome of patients undergoing lobectomy.

Keywords: lobectomy, mortality, morbidity, length of stay, healthcare delivery, patients' socioeconomic status, predictors of mortality and morbidity, Nationwide Inpatient Sample (NIS) database.
PUB004 PREOPERATIVE THERAPY IS NOT REQUIRED FOR CLINICALLY OCCULT N2 NON-SMALL CELL LUNG CANCER

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Background: Patients with clinically evident N2 NSCLC are usually treated by definitive chemoradiation or by resection following neoadjuvant therapy. To date, no clinical trials compared survival differences between induction and adjuvant therapy for occult N2 disease. We tested the hypothesis that patients with occult-N2 have equivalent survival after either neoadjuvant or adjuvant therapy. Methods: A retrospective review of a prospective database (2005-2014) was performed to identify patients with CT/PET negative mediastinal nodes, who were subsequently found to have positive N2 nodes either by mediastinoscopy or after resection. Demographic, clinical, and pathological data were reviewed. Disease free survival (DFS) was analyzed using Kaplan-Meier and differences compared using log-rank. Cox proportional hazards regression analysis was performed to determine the independent predictors of DFS. Univariate predictors (p<0.20) were selected for inclusion in a multivariate model. Results: Among 1693 patients with cN0-cN1 by PET/CT, 116 (6.8%) had pathologically confirmed N2 disease, of whom 101 had surgical resection. Fifteen two patients had mediastinoscopy, of whom 20 (38%) were positive and received induction chemotherapy followed by surgical resection. Surgical resection followed by adjuvant chemotherapy was done in the remaining 81 patients. There was no difference between the induction and no induction groups in clinical variables (Table1), the number of positive mediastinal nodal stations (median 1 in both groups, p=0.605), or in 5 years DFS (31% vs. 36%, p=0.644) (Fig1). In the multivariate model of the whole cohort, timing of chemotherapy (preoperative or adjuvant) was not associated with worse DFS, while increased clinical tumor size was the strongest predictor of worse DFS (HR=1.47, CI: 1.16-1.85, p=0.001). Conclusion: Patients with NSCLC and clinically occult N2 by PET/CT maybe treated by primary surgical resection followed by adjuvant chemotherapy. Invasive mediastinal staging in this setting has a low sensitivity and is not necessary.

Keywords: lobectomy, morbidity, Length of stay, mortality

PUB005 ROBOTIC THYMECTOMY: COMPARABLE PERIOPERATIVE OUTCOMES FOR BENIGN LESIONS AND EARLY STAGE THYMIC TUMORS

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Background: Recently, robotic assisted thymectomy (RAT) has emerged as an alternative to either, an open trans-sternal approach (TT) or to a video assisted thoracoscopic (VATS) approach, for both thymic tumors and non-tumor lesions. Proponents of the robotic approach have highlighted a decrease in postoperative morbidity and length of stay. We have reviewed our early experience with RAT and examined the differences in perioperative outcomes between patients with benign lesions and early stage thymic tumors. Methods: A prospectively collected database was reviewed for patients who underwent RAT for all causes between 2012-2015. Perioperative outcomes including operative time, blood loss, chest drainage, perioperative complications, length of stay, and pathological results were retrieved and analyzed. Results: 60 patients (41 females) with a median age of 53, underwent RAT. On presentation, 19 patients (32%) had myasthenia gravis (MG), 8 patients (13%) had MG with a concomitant mediastinal mass, and 33 patients (55%) had an enlarged mediasternal mass. The median operative time was 88 min (74-126) with 5 conversions to an open approach for local invasion (n=3) or for complete pleural symphysis (n=2). There were 2 rib fractures and 1 recurrent laryngeal nerve palsy. Median length of chest tube drainage and length of stay were 1 day (1-2) and 3 days (2-4) respectively. Three patients had post-operative MG crises, 3 had a pneumonia, and 2 had a residual pneumothorax. There were no perioperative mortalities. There were no differences in operative time (p=0.412), blood loss (p=0.813), duration of chest tube drainage (p=0.120), length of stay (p=0.896), intraoperative complications (p=0.962), or postoperative complications (p=0.510) between patients who had thymic tumors on final histopathological analysis [29 patients (48%)], and those who had thymic hyperplasia/benign cysts (n=31) (Table). Conclusion: Robotic thymectomy is feasible and safe for resection of both non-thymomatous and early thymic tumors, and is associated with a favorable perioperative outcome.

Keywords: robotic, thymectomy, Thymic tumors

PUB006 IMPACT OF THE NEW WHO CLASSIFICATION OF THYMIC TUMORS: CROSS-VALIDATION OF THE PROGNOSTIC VALUE IN A SINGLE INSTITUTION COHORT

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Background: The prognostic value of the histological classification of thymomas has long been questioned. The new 2015WHO classification (4th edition), that has recently been published, has refined the diagnostic criteria for thymoma subtypes. In the current study, we sought to explore the
ALK inhibitors (lorlatinib and ASP3026) are also being evaluated in clinical trials overcoming known ALK resistant mutations. On the other hand, with the development of high-throughput sequencing, called next-generation sequencing (NGS) and genomic technologies, more novel molecular targets such as MET 14 exon skipping splicing mutations have been identified as potential therapeutic targets and simultaneously analyzing hundreds of molecular alterations have turned out reality with limited tumor tissues. In the recent years, the emergence of numbers of oncogenic drivers other than EGFR mutations and ALK rearrangements has divided NSCLC into multiple distinct subtypes amenable to corresponding targeted therapy. For instance, dabrafenib either as monotherapy or in combination with MEK inhibitor (trametinib) has displayed promising antitumor activity and manageable safety profile in patients with BRAF V600E mutations, accounting for around 1.4% of patients with NSCLC. Other novel molecular targets maybe serving as oncogenic drivers including mutations in HER2 (erbB2) and its tyrosinase (tyr) and PI3KCA (BKMY120 and DCD0941), ROS1 (entrectinib, foretinib and lorlatinib), RET (XL184) and NTRK (entrectinib) rearrangements and FGFR1 gene amplification (AZD4547, Lenvatinib and FP-1039) are being evaluated either in preclinical settings or early-stage clinical trials. Methods: Section not applicable; Results: Section not applicable; Conclusion: Section not applicable.

Keywords: non-small cell lung cancer; EGFR; ALK; novel TKIs

PUB008 1,000 VIDEO-ASSISTED THORACOSCOPIC LOBECTOMIES (VATS): A SINGLE INSTITUTION’S EXPERIENCE
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Thoracic Division of Cardiothoracic Surgery Department, Weill Cornell Medical Center-NY Presbyterian Hospital, New York/NY/United States of America

Background: Despite recent increase in VATS adoption for major lung resection. Reports derived from large national registries show underutilization of this approach nationwide. To date, no randomized trials have directly compared VATS to a thoracotomy approach. We sought to review our experience with 1000 VATS lobectomy (lobectomy using VATS approach (2002-2014). Survival was estimated using Kaplan Meier analysis. Cox regression multivariable analysis (MVA) was used to identify independent predictors of DFS. Results: In the study period, 1009 VATS lobectomies were performed (median age 71 yr, 40% were males). The clinical and pathological characteristics of the cohort studied are listed (Table). Median postoperative length of stay (LOS) was 4 days with 27% discharged ≤ 3 days. Median operative time (OR) and estimated blood loss (EBL) were 131 minutes and 100 cc respectively. Conversion to a thoracotomy was encountered in 66 patients (6.5%). 3 patients (0.3%) had 30-days post-operative mortality. On MVA, only advanced pathological stage, (pStage II, HR: 1.69, 95% CI: 1.15-2.48), (pStage III, HR: 2.94, 95% CI: 2.09-4.14), grade 2/3 tumors (HR: 1.53, 95% CI: 1.19-2.16), and longer LOS (HR: 1.05, 95% CI: 1.01-1.09) independently predicted poor DFS. A subgroup analyses on 150 patients (14.9%) 80 years old or older (octogenarians), showed comparable complications rate with their younger counterparts (80 years old) (Clavien Dindo ≥ 3, 22.7% vs 17.2%, p=0.110), despite having significantly higher Charlson comorbidity index (CCI:1.46.7% vs 34.3%, p=0.006). Also, there were no differences between patients older and younger than 80 years old regarding probability of freedom from recurrence (p=0.457) or cancer specific survival (p=0.305). Conclusion: The current study reports a large number of lobectomies performed using VATS approach in a high volume academic center. These data came in accordance with previous reports affirming the feasibility, safety, and improved perioperative outcomes associated with this approach, even in the frail octogenarians.

Keywords: WHO Classification, Prognosis, Thymoma

PUB007 NOVEL TKIS IN NON-SMALL CELL LUNG CANCER
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Background: The presence of EGFR activating mutations and ALK chromosomal rearrangements with corresponding tyrosine kinase inhibitors (TKIs) has revolutionized the treatment strategies of patients with non-small cell lung cancer (NSCLC). Although tremented initial response and manageable toxicity profiles, acquired resistance inevitably develops after approximately 1 year treatment with EGFR-TKIs (erlotinib and gefitinib) and ALK inhibitor (crizotinib). Encouragingly, third-generation EGFR-TKIs such as AZD9291, CO1686 and brigatinib have showed striking efficacy with ALK inhibitor (crizotinib). Overcoming acquired resistance driven by T790M secondary mutations. Other novel third-generation TKIs including AZD9291, CO1686 and brigatinib are also being investigated in early-stage clinical trials and the survival and safety data will be released in the near future. Another promising EGFR-TKI, namely AZD3759 has showed promising response in patients with brain metastases and leptomeningeal disease. Recently, EA1045, an EGFR allosteric inhibitor, in combination with cetuximab exhibit antitumor activity in mouse models of lung cancer driven by L858R/T790M/C797S, a resistant mutation of AZD9291. Meanwhile, second-generation ALK inhibitors (ceritinib and alectinib) have entered clinical applications for NSCLC patients with ALK rearrangements after failure of crizotinib and third-generation ALK inhibitors (lorlatinib and ASP3026) are also being evaluated in clinical trials.
PUB009 NEW CHEMOTHERAPY REGIMEN; DOES IT REALLY WORK FOR ESOPHAGEAL CANCER ADENOCARCINOMA?

M Rahouma1, Barry Kaplan2, Mohamed Kame1, Galal Ghaly1, Paul Lee3

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Background: Neoadjuvant chemotherapy for esophageal cancer changed over last years with the current most used regimen being EOX(Epirubicin, Oxaloplatin & Xeloda) for adenocarcinoma but this treatment still carries many adverse events(AE) as identified by NCI-CTCAEv.4. Among R0(complete resection) group, we sought to investigate a modification for current ones seeking a better response rate, lower AE rate and better quality of life(QoL).

Methods: This is a pilot study(Sep.2008-Dec.2014) involving Taxol/Carboplatin/Xeloda/TCX(paclitaxel 80mg/m^2 days 1 and 8, carboplatin 5AUC day 1, capecitabine 750mg/m^2 BID for 14 days){Ruoff, C.A.,Hong,B.,Kaplan,et al,Single-center experience with paclitaxel(T),carboplatin(C),and capecitabine(X) in treatment of advanced esophagogastric cancer.In ASCO-Gastrointestinal Cancer Symposium, 2013;116}. Patients were followed through chemotherapy course to capture grade 1,2,3,4 and 5 AE(Mild, Moderate, Severe, Life-threatening and Death respectively). Kaplan-Meier survival curves were used to calculate disease free survival(DFS). QoL was assessed using Functional Assessment of Cancer Therapy-Esophagus(FACT-E) questionnaire 12 months or more post-operatively. Results: Among our database, 8 patients received neoadjuvant-TCX for adenocarcinoma with median age 61(51-75) years, BMI28.8(20.1-33.6). Most patients were male, performance status of 0(7 patients). They had lower or GEJ-adenocarcinoma predominantly(7 patients). Clinical stage I/II and III were present in 2 and 6 patients respectively. Pathological stage I,II and III were present in 3, 3 and 2 patients respectively. Median pre-induction PET-standardized uptake value(PET-SUV) was 10.1 vs 3.6 post-induction(p=0.014) with median PET-SUV decrease percent of 75.3%. 87.5% were clinical responder(>50% decrease) and 75% were radiological responder(>50% decrease in PET-SUV). 25% of our cohort received adjuvant treatment. Grade 2 toxicity occurred in 44.4% of the patients(37.5% grade 2, 12.5% grade 3 and none had grade 4 or 5). Hematologic AE were the most frequent(anemia 87.5%, neutropenia 50%(grade 1,2, and 3 in 2,1 and 1 patients respectively), leukopenia 25% and thrombocytopenia 37.5%) followed by diarrhea(25%). No patient had neutropenic sepsis. Mean DFS was 66 months. 3 and 5-years DFS was 87.5 and 72.9% respectively( Figure 1A). Conclusion: TCX is a novel, safe regimen and carries a low AE rate(mostly low grade AE). It is associated with reasonable DFS and better QoL. However, large scale RCT is necessary and warranted.

<table>
<thead>
<tr>
<th>Patients characteristics</th>
<th>Number(%)/ Median(IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Stage I</td>
<td>761(75.6%)</td>
</tr>
<tr>
<td>Clinical Stage II</td>
<td>130(12.9%)</td>
</tr>
<tr>
<td>Clinical Stage III</td>
<td>116(11.5%)</td>
</tr>
<tr>
<td>Pathological Stage I</td>
<td>763(75.6%)</td>
</tr>
<tr>
<td>Pathological Stage II</td>
<td>130(12.9%)</td>
</tr>
<tr>
<td>Pathological Stage III</td>
<td>116(11.5%)</td>
</tr>
<tr>
<td>PFTs FEV%</td>
<td>80(77-104)</td>
</tr>
<tr>
<td>PFTs FVC%</td>
<td>79(80-102)</td>
</tr>
<tr>
<td>PFTs DLCO%</td>
<td>83(68-99)</td>
</tr>
<tr>
<td>Resected lobe laterality</td>
<td></td>
</tr>
<tr>
<td>Rt side</td>
<td>612(60.7%)</td>
</tr>
<tr>
<td>Lt side</td>
<td>397(39.3%)</td>
</tr>
<tr>
<td>Grade of differentiation</td>
<td></td>
</tr>
<tr>
<td>Well differentiated</td>
<td>236(23.4%)</td>
</tr>
<tr>
<td>Poor differentiated</td>
<td>773(76.6%)</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>813(80.6%)</td>
</tr>
<tr>
<td>Squamous cella</td>
<td>121(12%)</td>
</tr>
<tr>
<td>Others</td>
<td>75(7.4%)</td>
</tr>
<tr>
<td>Complications</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>747(74%)</td>
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<tr>
<td>Yes</td>
<td>262(26%)</td>
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<tr>
<td>Clavin Dindo Class(CDC)</td>
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<tr>
<td>CDC2</td>
<td>194(19%)</td>
</tr>
<tr>
<td>Length of stay(days)</td>
<td>4(3-5)</td>
</tr>
<tr>
<td>OR time(minutes(n=556))</td>
<td>131(103-162)</td>
</tr>
<tr>
<td>Estimated blood loss(ml(n=564))</td>
<td>100(50-200)</td>
</tr>
</tbody>
</table>

Keywords: VATs lobectomy, non-small cell lung cancer; NSCLC, Octogenarian, Charlson comorbidity index

B) Quality of life(Our cohort vs Literature)

<table>
<thead>
<tr>
<th>Mean Score for</th>
<th>Our Cohort</th>
<th>Safieddine et al,2009*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical well-being (PWB)</td>
<td>26.4</td>
<td>22.5</td>
</tr>
<tr>
<td>Social well-being (SWB)</td>
<td>27.9</td>
<td>NA</td>
</tr>
<tr>
<td>Emotional well-being (EWB)</td>
<td>22.1</td>
<td>NA</td>
</tr>
<tr>
<td>Functional well-being (FWB)</td>
<td>26.4</td>
<td>20</td>
</tr>
<tr>
<td>FACTG</td>
<td>102.9</td>
<td>NA</td>
</tr>
<tr>
<td>ECO</td>
<td>66.4</td>
<td>55</td>
</tr>
<tr>
<td>TOTAL</td>
<td>169.3</td>
<td>138.6</td>
</tr>
</tbody>
</table>

Keywords: New chemotherapy regimen, FACT-E questionnaire, esophageal cancer

PUB010 INTRAOPERATIVE BLOOD LOSS IS AN INDEPENDENT PREDICTOR OF POOR DISEASE FREE SURVIVAL FOR PATIENTS UNDERGOING VATS LOBECTOMY FOR LUNG CANCER
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Background: There are concerns regarding the independent effect of intra-operative estimated blood loss (EBL) on the oncological outcome of patients undergoing lung cancer surgery. A negative immunomodulatory effect has been hypothesized. These effects have been observed after conventional open surgery. Little is known in regards to the impact of blood loss in a VATS approach on outcome. Therefore, we sought to assess the effect of intraoperative blood loss on disease free survival for a select subset of patients undergoing VATS lobectomy for NSCLC. Methods: A prospectively collected lung cancer database was retrospectively reviewed to identify patients undergoing VATS lobectomy for NSCLC (2009-2016). Clinico-pathological characteristics and follow up data were retrieved from the database as well as the patients’ medical records. Cox regression analysis was used to identify independent predictors of disease free survival (DFS). Results: In the study period, 551 VATS lobectomies were done (median age 72 years, 35% were males). Median Charlson comorbidity index (CCI) was 1. Median FEV1% and DLCO% were 91% and 83% respectively. The majority of patients were clinical stage 1 (459 patients, 83.3%; 3yr DFS: 85.5%). 20% of the patients had adenocarcinoma histology, and moderately/poorly differentiated tumors represented 83%. Median OR-time and EBL were 132 minutes and 100 CC respectively. Conversion to thoracotomy was encountered in 30 patients (5.4%). 148 patients (26.9%) had post-operative complications [Clavien-Dindo (CD) ≥ 3]. Reoperation was needed in 9 patients (1.6%). 3 patients (0.5%) had 30-days postoperative mortality. Univariate predictors of poor DFS were age, female sex, current smoking, clinical stage III, moderate/poor differentiation, right side lobectomies and EBL ≥ 250cc. On multivariable analysis only male gender (HR: 1.79, 95% CI: 1.16-2.70), and EBL ≥ 250cc (HR: 1.65, 95% CI: 1.04-2.61) independently predicted poor DFS. Conclusion: In patients undergoing VATS lobectomy for NSCLC, EBL was the only modifiable predictor of poor DFS. The results of this study should be cautiously interpreted and needs to be furtherly validated in larger data sets.

Keywords: RET, Targeted therapy, Acquired resistance, VEGFR2-sparing

PUB012 INHIBITION OF THE COLONY-STIMULATING-FACTOR-1 RECEPTOR AFFECTS THE RESISTANCE OF LUNG CANCER CELLS TO CISPLATIN
Mario Cicco, Carmencita Lavilla, Chandra Goparaju, Harvey Pass
NYU Langone Medical Center, New York/New York/United States of America

Background: Colony-Stimulating-Factor-Receptor-1 (CSF-1R) is a type III receptor tyrosine kinase (RTK) responsible for promoting the differentiation, survival and homing of the monocytic-macrophage cell lineage. Here we provide evidence for the existence of cisplatin-resistant, lung cancer cell subpopulations expressing the Colony Stimulating Factor Receptor-1 (CSF-1R). Methods: CSF-1 and IL-34 secreted from A549, H1299, H1975, CALU-1, NCI-H157, NCI-H358, NCI-H460 were measured. ALDH-positive cells were defined as cells that displayed greater fluorescence compared with a control staining reaction containing the ALDH inhibitor, DEAB upon addition of synthetic ALDH substrate BAAA. siRNA CSF-1 and siRNA IL-34 were transfected into lung cancer cells. (CSF-1R). siRNA targeting CSF-1R tyrosine kinase inhibitor (TKI) was provided by Janssen Research & Development. Results: QPCR of all but one cell line expressed detectable amounts of CSF-1R and IL-34. Western blotting with anti-CSF-1R antibodies confirmed extracellular and intracellular forms of the receptor in six out of seven cell lines. ELISA revealed detectable levels of secreted CSF-1 and non-detectable IL-34. QPCR of mRNA obtained from H1975, NCI-H1299, A549 and Calu-1 revealed that both the receptor and the ligand CSF-1 mRNA were increased by cisplatin treatment, and conditioned medium from the same cells revealed increased levels of CSF-1 from cisplatin treated ones. Significantly impaired colony formation in cells transfected with siRNAs directed towards CSF-1 or CSF-1R occurred and was strongly increased by cisplatin treatment at subtoxic doses. Co-treatment of the cells with increasing doses of cisplatin and (CSF-1R) revealed a strong potentiation of cisplatin cytotoxicity. FACs analysis revealed 4/4 representative lung cancer cell lines contained ALDHbright cells and exhibited increased number of ALDHbright cells upon cisplatin treatment, and (CSF-1R) increases significantly the number of ALDHbright cells. This effect was much stronger when the TKI was administered to the cells in combination with cisplatin. Treatment of tumor bearing mice with (CSF-1R) produced strong chemo-sensitizing effects in vivo and this correlated with a reduced number of CSF-1Rpos cells in tumors excised from the treated mice. Depletion of the CD45pos cells within the treated tumors did not, apparently, play a major role in the tumor growth.

Keywords: Gender differences, intraoperative estimated blood loss (EBL), non-small cell lung cancer, NSCLC, Disease free survival (DFS)

PUB011 A POTENT, VEGFR2-SPARING RET KINASE INHIBITOR FOR TREATING PATIENTS WITH RET-DEPENDENT LUNG CANCERS
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Background: Activating mutations and fusions of the RET receptor tyrosine kinase have been identified in several cancer types, including fusions in ~2% of lung adenocarcinomas. Furthermore, tyrosine kinase inhibitors (TKIs) that inhibit RET have activity in patients with RET-dependent cancers. However, current TKIs are only moderately potent against RET, cause toxicity through stronger inhibition of other kinases (e.g. KDR/VEGFR2) and poorly inhibit secondary resistance (e.g. gatekeeper mutations). We aimed to design an inhibitor that targets diverse RET fusions and potential resistance mutations, with sparing of anti-targets and excellent drug-like properties. Methods: Lead RET inhibitor candidates were selected by determining: (1) activity against KDR- and CCDC6-RET fusions and in lung cancer cell lines and (2) V804 gatekeeper substitutions that cause acquired resistance to multikinase inhibitors, and (2) selectivity against a broad panel of kinase and other anti-targets. Activity in vivo was determined by measuring both pharmacodynamic target modulation and efficacy in diverse RET-dependent tumor models, including cancer cell line and patient-derived mouse xenografts (PDX). Results: 6 potent lead RET candidates possess nanomolar potency against diverse RET fusions and potential acquired resistance mutations, including challenging V804 gatekeeper substitutions. Furthermore, each is at least 100-fold selective for the majority of kinases analyzed in vitro, and this high degree of selectivity against critical targets in live cells suggests that the properties lead to significant efficacy in vivo in lung cancer xenografts harboring endogenous RET alterations and a RET-fusion PDX with acquired resistance to multikinase inhibitors mediated by V804M. Finally, daily oral dosing of mouse xenografts for more than three months produces continued tumor regression, without the development of acquired resistance or toxicity. The unique combination of high potency, broad activity against diverse RET alterations and minimal activity against anti-targets indicates the potential for continuous dosing, long-term efficacy and a wide therapeutic index in the clinic. Conclusion: We have identified a new series of potent and specific RET inhibitors with favorable pharmaceutical properties and potent activity against diverse RET alterations in vitro and in vivo, including founder genetic alterations and resistance mutations that may arise following treatment with multikinase inhibitors. Together with significant sparing of other kinase and non-kinase anti-targets, they are predicted to robustly inhibit RET in patients at clinically relevant doses, and therefore offer the potential for more effective and safe treatment of patients with RET-dependent cancers. Loxo Oncology will be initiating clinical development of its lead RET inhibitor in patients with RET-fusion lung cancers in the coming months.

Keywords: RET, Targeted therapy, Acquired resistance, VEGFR2-sparing
Inzai/Japan, Japan and six showed PD. There were no treatment related toxicities leading to the pembrolizumab alone arm vs 33.3% in the combination arm. In the were evaluable for the primary endpoint: 13 in the pembrolizumab alone arm vs 19 in the combination arm respectively. Results: From July 2015 to June 2016, 38 patients were randomized and 28 patients were evaluable for the primary endpoint: 13 in the pembrolizumab alone arm vs 15 patients in the combination arm. ORR at 12 weeks was 23.1% in the pembrolizumab alone arm vs 33.3% in the combination arm. In the pembrolizumab alone arm three patients had a confirmed partial response (PR); two had stable disease (SD) and eight showed progressive disease (PD). In the combination arm five patients had a confirmed PR; four had SD and six showed PD. There were no treatment related toxicities leading to discontinuations. Pembrolizumab and SBRT did not result in higher toxicity. Conclusion: SBRT on a single metastasis directly followed by pembrolizumab results in a promising ORR advantage in this preliminary analysis without an increase in toxicity.

Keywords: Immuno therapy, NSCLC, SBRT, pembrolizumab

PUB015 THE USE OF IMMUNOHISTOCHEMISTRY IMPROVES THE DIAGNOSIS OF SCLC. AN INTERNATIONAL REPRODUCIBILITY STUDY IN A DEMANDING SET OF CASES


Background: Immune checkpoint inhibitors have provided long-lasting responses in recurrent non-small cell lung cancer (NSCLC) patients, but the majority of patients do not benefit with response rates of <25%. To test if stereotactic body radiation therapy (SBRT) on a single metastasis preceding pembrolizumab, an anti PD-1 antibody, is safe and will lead to an increased tumor specific immune response, we initiated the multicenter phase II PEMBRO-RTO study. Methods: Patients with advanced NSCLC with all histologies, line one or further, regardless of PD-L1 status were randomized (1:1) between receiving iv. pembrolizumab (200mg q3w) alone or iv. pembrolizumab (200mg q3w) after SBRT (3x8Gy) on a single metastasis. Biopsies were taken from a non-irradiated tumor site at baseline and after two cycles of pembrolizumab. The primary endpoint was an improvement of the overall response rate (ORR) from 20% to 50% at 12 weeks in the pembrolizumab alone vs the combination arm respectively. Results: From July 2015 to June 2016, 38 patients were randomized and 28 patients were evaluable for the primary endpoint: 13 in the pembrolizumab alone arm vs 15 patients in the combination arm. ORR at 12 weeks was 23.1% in the pembrolizumab alone arm vs 33.3% in the combination arm. In the pembrolizumab alone arm three patients had a confirmed partial response (PR); two had stable disease (SD) and eight showed progressive disease (PD). In the combination arm five patients had a confirmed PR; four had SD and six showed PD. There were no treatment related toxicities leading to discontinuations. Pembrolizumab and SBRT did not result in higher toxicity. Conclusion: SBRT on a single metastasis directly followed by pembrolizumab results in a promising ORR advantage in this preliminary analysis without an increase in toxicity.

Keywords: Immuno therapy, NSCLC, SBRT, pembrolizumab

PUB016 NIVOLUMAB-INDUCED ACUTE LUNG INJURY IN NON-SMALL CELL LUNG CANCER PATIENTS

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Background: Nivolumab (Nivo) is a promising and hopeful drug for patients with advanced lung cancer. It is one of immune checkpoint inhibitors that play an important role in cancer therapy. Methods: In this report, we present three patterns of nivo-induced acute lung injury that have experienced in Japan. Results: From April 2015 to December 2016, 67 patients with advanced lung cancer states that a diagnosis of small cell lung carcinoma (SCLC) can be reliably made on routine histological and cytological grounds, but immunohistochemistry may be required for confirmation of neuroendocrine and epithelial nature of the tumor cells. In addition, in small biopsies, the proper assessment of activity of Ki-67 by IHC assessed by the pathologist should be performed to avoid misdiagnosing carcinoid tumors in the presence of crush artifact. However, reproducibility studies on H&E alone for SCLC versus large cell neuroendocrine carcinoma have shown pairwise kappa scores ranging from 0.35 – 0.81. In the diagnostic process of SCLC, IHC may be useful in such cases where histologic features are equivocal. However, the pathologist wants to gain confidence. This study examines whether judicious use of immunohistochemistry (IHC) improves diagnostic reproducibility for SCLC. Methods: Nineteen lung pathologists studied interactive digital images of 79 tumors predominantly neuroendocrine lung tumors. Rejection and biopsy sample images were diagnosed solely on morphology (level 1), morphology along with requested immunohistochemical stains (level 2), and with all available immunohistochemical stains (level 3). Results: For the 19 pathologists reading all 79 cases the agreement rate for level 1 was 64.7% and increased to 73.2% and 77.5% in levels 2 and 3, respectively. With IHC, kappa scores for four tumor categories (SCLC, LCNEC, carcinoid tumors, and other) increased in resection samples from 0.43 to 0.60 and in biopsy samples from 0.43 to 0.64. An approach for IHC in the differential diagnosis of SCLC is provided and needs further confirmation, preferably linked to treatment outcome. Conclusion: In this set of challenging cases H&E stand...
### PUB016 A MULTI-NATIONAL COHORT VALIDATION OF PROCEDURE-SPECIFIC NOMOGRAMS TO PREDICT RECURRENCE FOR SMALL LUNG ADENOCARCINOMAS

**Tarina Bains**, Kaitlin Woo, William Travis, Kay See Tan, David Jones, Prasad Adusumilli

**Thoracic Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York/NY/United States of America, 2Institute of Pathology, Heidelberg University Hospital, Heidelberg/Germany, 3Department of Pathology and Laboratory Medicine, Taipei Veterans General Hospital, Taipei/Taiwan, 4Department of Thoracic Surgery, The University of Tokyo Hospital, Tokyo/Japan, 5Department of Surgery, Taipei Veterans General Hospital, Taipei/Taiwan, 6Department of Diagnostic Pathology, Kagawa University, Kagawa/Japan, 7Department of Pathology, Memorial Sloan Kettering Cancer Center, New York/NY/United States of America

**Background:** The purpose of this study was to construct and validate procedure-specific nomograms, using competing risk analysis, to predict recurrence following resection for lung adenocarcinoma (LADC) ≤2 cm. Methods: Nomogram development was performed using an internal cohort (N=909) of patients who underwent R0 resection for small LADC at our institution (Table 1), and external validation was conducted using cohorts (N=708) from Japan, Taiwan, and Germany. Cumulative incidence of recurrence (CIR) was assessed, treating death without recurrence as a competing risk. Nomograms for 5-year-CIR were developed using significant prognostic factors from multivariable analyses and were evaluated internally using bootstrap validation. The predictive accuracy of the nomograms was measured using a concordance index (C-index). **Results:** Multivariable analyses identified six independent risk factors with the highest predictive accuracy for CIR in both the LO (lobectomy) and LR (limited resection) groups (Table 2). These variables were used to develop two nomograms with C-index of 0.747 for LO and 0.748 for LR. The two nomograms were validated externally with high accuracy (C-index of 0.710 for LO and 0.796 for LR). **Conclusion:** The two procedure-specific nomograms with high C-indices can be used to predict recurrence and, thereby, better prognosticate and stratify patients with resected small LADC by outcomes.

**Keywords:** Nomogram, STAS, Adenocarcinoma, competing risk

### PUB017 MINIMALLY INVASIVE LOBECTOMY IS ASSOCIATED WITH LOWER NONCANCER SPECIFIC MORTALITY IN ELDERLY: A PROPENSITY-SCORE MATCHED ANALYSIS

**Boris Hristov**, Takashi Eguchi, James Isbell, Bernard Park, Kay See Tan, Valerie Rusch, David Jones, Prasad Adusumilli

**Thoracic Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York/NY/United States of America, 2Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York/NY/United States of America

**Background:** Two-thirds of the patients with non-small cell lung cancer (NSCLC) are elderly (>65 years). As age increases, the risk of competing events, such as noncancer death, increases. The aim of this study is to investigate cancer- and noncancer-specific mortality following lobectomy by minimally invasive surgery (MIS, includes VATS and robot-assisted thoracotomies) versus thoracotomy in elderly patients with NSCLC. **Methods:** Of 2208 patients who underwent curative-intent lobectomy for pStage I-III NSCLC without induction therapy (2000-2012), 1458 patients (66%) were ≥65 years of age and included in the analysis. Of these, 466 patients underwent MIS and 992 underwent thoracotomy. Propensity-score matching was performed to identify pairs of thoracotomy and MIS patients with comparable clinical characteristics including types of comorbidities, pulmonary function, pathological stage, tumor size, and year of surgery. Association between surgical approach (MIS vs. thoracotomy) and cause-specific mortality analysis was performed using competing risks approaches: Kaplan-Meier CIDE curves, and Fine and Gray's test to quantify the effects of surgical approach. **Results:** Following propensity matching of patients who underwent thoracotomy (N=366) versus MIS (N=366), there were statistically significant differences in length of stay (p<0.001), 90-day mortality (p<0.046), 1-year mortality (p=0.018), and noncancer-specific mortality (p=0.036). There was no difference in lung cancer-specific mortality. In multivariable analysis, thoracotomy (vs. MIS) was an independent risk factor for noncancer-specific death – HR 2.99 (95% CI 1.32-6.76, p = 0.009). **Conclusion:** In a propensity-score matched cohort, multivariable analysis indicates that lobectomy performed by minimally-invasive means is associated with lower incidence of noncancer-specific mortality compared to lobectomy performed by open thoracotomy in elderly patients with NSCLC.

**Keywords:** Nomogram, Concordance index, risk adjustment, surgical approach, outcomes
PUB019 PREOPERATIVE NEEDLE BIOPSY AND TUMOR SPREAD THROUGH ALVEOLAR SPACES (STAS) IN RESECTED LUNG ADENOCARCINOMAS

Koji Kameda1, Takashi Eguchi1, Shaohua Lu2, Stephen Solomon2, Matthew Bott1, David Jones1, Natasha Rekhtman2, William Travis2, Prasad Adusumilli3
1Thoracic Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York/NY/United States of America, 2Department of Pathology, Memorial Sloan Kettering Cancer Center, New York/NY/United States of America, 3Department of Radiology, Memorial Sloan Kettering Cancer Center, New York/NY/United States of America

Background: We investigated whether preoperative needle biopsy (NB) is associated with higher incidence of tumor spread through air spaces (STAS) and the association with recurrence pattern in resected lung adenocarcinomas (LADC). Methods: Patients who underwent curative-intent resection for ≤2 cm LADC (n=874, 1995-2011) were analyzed as 2 groups: NB and no-NB (diagnosed with frozen section). Patients diagnosed with transbronchial biopsy/cytology, and failed preoperative biopsy were excluded (n=66). Results: Of 808 patients, NB group (n=465: fine-needle aspiration (FNA), n=356; core-needle, n=44; both, n=65) of patients are associated with higher age, and larger tumor size than no-NB (n=343). There was no difference in the incidence of STAS in the resection specimens and other pathological findings between the groups. Among patients with STAS(+), tumors, no difference in recurrence was noted in patients who underwent lobectomy, in patients with sublobar resection, probability of local recurrence was significantly higher in NB group compared to no-NB, with no difference in regional or distant recurrence. No difference was observed in any recurrence pattern in STAS(+) cases regardless of the type of resection.

Conclusion: Pre-operative needle biopsy is not associated with increased incidence of STAS. In patients who underwent sublobar resection, larger cohort analysis by FNA, core or both biopsies is required.

Comparison between NB vs. no-NB

<table>
<thead>
<tr>
<th></th>
<th>NB N=465 (%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>66.3</td>
<td>0.001</td>
</tr>
<tr>
<td>Sex</td>
<td>212 (62)</td>
<td>0.970</td>
</tr>
<tr>
<td>Smoking</td>
<td>131 (38)</td>
<td>0.112</td>
</tr>
<tr>
<td>Former Current</td>
<td>230 (69)</td>
<td>0.386</td>
</tr>
<tr>
<td>Surgery Lobectomy</td>
<td>206 (60)</td>
<td>0.770</td>
</tr>
<tr>
<td>Sublobar resection</td>
<td>137 (40)</td>
<td>1.5</td>
</tr>
<tr>
<td>Tumor Size (cm)</td>
<td>1.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lymphatic invasion</td>
<td>108 (31)</td>
<td>0.452</td>
</tr>
<tr>
<td>Vascular invasion</td>
<td>72 (19)</td>
<td>0.046</td>
</tr>
<tr>
<td>Pleural invasion</td>
<td>50 (15)</td>
<td>0.493</td>
</tr>
<tr>
<td>STAS</td>
<td>127 (37)</td>
<td>0.065</td>
</tr>
<tr>
<td>Recurrence Local</td>
<td>8 (2)</td>
<td>0.170</td>
</tr>
<tr>
<td>Regional</td>
<td>20 (6)</td>
<td>0.400</td>
</tr>
<tr>
<td>Distant</td>
<td>31 (9)</td>
<td>0.313</td>
</tr>
<tr>
<td>Pleural/Chest wall</td>
<td>13 (4)</td>
<td>0.020</td>
</tr>
</tbody>
</table>

Recurrence free probability curves: NB vs. no-NB by recurrence pattern and STAS in patients following sublobar resection (N=318)

PUB020 SAME DAY CT FOR THE BRONCHOSCOPIC DIAGNOSIS OF SPN MAY DECREASE UNNECESSARY PROCEDURES IN

Keywords: biopsy, diagnosis, sublobar resection, recurrence

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CARCINOMAS AMONG THE CYTOLOGY POSITIVE PATIENTS

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Institute of Nuclear Medicine and Allied Sciences, Rajshahi/Bangladesh

Background: Over the last decades, due to the widespread availability, low financial cost, non-invasiveness and a zero ionizing radiation effect, ultrasound is used as the leading medical imaging modality for the initial diagnostic work-up of various multi-organ medical disorders including lung related pathologies like pleural effusion, lung growths etc. And its basic display mode (which is called the brightness mode) reflects different degrees of echogenicity, depending upon the study organs, areas and their underlying pathologies. It can also be done either as trans-wall or endo-luminal means along with the capability of vascular blood flow study. While low dose computed tomography can also be done either as trans-wall or endo-luminal means along with the capability of vascular blood flow study. While low dose computed tomography is used primarily as the screening test among the high-risk population groups for lung cancer detection, ultrasonography (as a stand-alone modality or as the part of hybrid imaging technique) can be used as a convenient guide for the collection of small biopsies from which efficient interpretation regarding cytological classification and molecular typing are performed as state of the art technology. Methods: This study was conducted at the Institute of Nuclear medicine and Allied Sciences, Rajshahi and the period between 1st May, 2009 and 31st October, 2010. The patients having positive lung lesions on digital radiography are referred to this institute by the clinicians for ultrasonography of chest and transthoracic ultrasonography-guided fine-needle aspiration biopsy (FNAB) cytological examination, with the co-operation of pathology department of Rajshahi Medical College, Rajshahi, Bangladesh. Under the basis of convenient sampling technique, 77 patients are included as sample. Their age, gender, sonographic echo-patterns of lung carcinomas and cytological findings are recorded and analyzed with statistical software IBM SPSS v. 16. Results: Among the sample (n=77), 67 (87%) were male and 10 (13%) were female. Mean ± SD age was 56 ± 14 years (range=28 to 85 years). Regarding the cytological findings, 30 (39%) had squamous cell carcinoma, 18 (23.4%) had undifferentiated large cell carcinoma and 17 (22.1%) had undifferentiated malignant epithelial tumor. And, in relation to the sonographic echo-pattern underlying a single cytology positive patient, 64% were echogenic, 33% were hypoechoic, 3% were anechoic, and 1% were mixed echo-pattern. Conclusion: The results of this study will be helpful toward the relevant studies which are related to the management algorithm of lung carcinomas, in addition to the role of hybrid imaging techniques as well as histologic classification, molecular typing, genetic and epigenetic profiling from the resected or imaging technique-guided taken small biopsies and cytology specimens.

Keywords: Sonographic echo-pattern, lung carcinomas, cytology positive.

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Abstracts

SUSPECTED LUNG CANCER PATIENTS

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Background: Bronchoscopy is commonly used for the diagnosis of solitary pulmonary nodules discovered on CT scanning of the chest. Initial imaging is often completed well before the date of a scheduled test, with repeat imaging generally not repeated prior to the diagnostic procedure. We report a series of resolving nodules seen on chest CT performed the day of electromagnetic navigation bronchoscopy, resulting in cancellation of the procedure. Methods: A prospective case series for patients undergoing navigational bronchoscopy using a new technology requiring same day CT imaging at a single quaternary care center. Patients undergoing navigational bronchoscopy found to have a decrease in the size or resolution of their nodule leading to the cancellation of their case were included. Included patients had demographic data, lung cancer risk factors as well as pre and day of CT imaging collected. Results: During the study period, 106 patients were scheduled for navigational bronchoscopy for the diagnosis of a pulmonary nodule. Of the 106 patients scheduled 7 (6.6%) had a decrease in the size of/or resolution of their nodule leading to the cancellation of their procedure. The average time from initial CT prompting referral for bronchoscopy to the day of procedure scan for those cancelled was 53 days. Conclusions: Time from initial imaging to day of procedure is variable, occasionally allowing enough time for nodules to resolve obviating the need for biopsy. Although bronchoscopy is a safe and well tolerated procedure, same day imaging may decrease unnecessary procedural risk.

Keywords: solitary pulmonary nodule, bronchoscopy.

PUBLIC DEVELOPMENT OF A LUNG CANCER AWARENESS INTERVENTION TARGETED AT SOCIOECONOMICALLY DEPRIVED COMMUNITIES IN WALES, UK

Grace McCutchan, Fiona Wood, Adrian Edwards, Stephanie Smits, Kate Brain School of Medicine, Division of Population Medicine, Cardiff/United Kingdom

Background: Lung cancer incidence is highest and survival lowest amongst people from socioeconomically deprived groups. Evidence from controlled studies suggests that although mass media lung awareness campaigns can lead to improved symptom awareness, symptom presentation behaviour and stage shift in lung cancer, campaign reach may be limited to more affluent groups. There is a need for interventions targeted at people in deprived communities to encourage earlier lung cancer symptom presentation. Community-based educational intervention has been identified as having the potential to engage harder to reach groups by challenging deep-seated negative beliefs about cancer through family and social networks. Methods: The Behaviour Change Wheel was used to guide intervention type, content and delivery. Barriers and enablers to lung cancer symptom awareness were identified from existing sources (a systematic review, qualitative interviews with thirty people living in deprived communities, and six focus groups with people who live or work in deprived communities in Wales) and mapped to the Behaviour Change Wheel. The intervention was tested for acceptability with a group of seven potential users: adults aged over 40 living in a deprived community, who were current/former smokers or family members of smokers. Data from user testing were analysed using observations and before/after questionnaires. Results: Mapping to the Behaviour Change Wheel suggested that face-to-face group education was a relevant mode of intervention, delivered by a trained, trusted member of the community. Intervention content was designed to address identified barriers and enablers included: information about lung cancer symptoms, the benefits of early diagnosis, action planning in the event of symptom experience, strategies to overcome barriers to cancer symptom presentation and aid communication of symptoms during a consultation, and information on how to spot symptoms in other people in the community and what advice should be given. Observations made during the intervention session confirmed that group education was an acceptable mode of intervention delivery. Suggested changes to the intervention included the addition of smoking cessation advice. Conclusion: A community-based educational intervention has been developed to increase lung cancer symptom knowledge, modify negative beliefs and encourage timely symptom presentation by utilising strong social networks in the community. Group-based education was an acceptable mode of intervention delivery among people in deprived communities, and warrants further feasibility and pilot testing. This research provides an important contribution to evidence regarding effective methods of engaging harder to reach groups in lung cancer early detection.

Keywords: cancer awareness intervention, lung cancer, socioeconomic group, patient delay.

PUBLIC EFFICACY OF THREE-DIMENSIONAL VIDEO SYSTEM IN SINGLE PORT THORACOSCOPIC MAJOR PULMONARY RESECTION: PROPENSITY SCORE MATCHED ANALYSIS

Hyun Koo Kim, Kook Nam Han, Young Ho Choi
Thoracic and Cardiovascular Surgery, Korea University Guro Hospital, Seoul/Korea, Republic of

Background: The aim of this study was to evaluate the surgical outcomes of video assisted thoracic surgery using a three dimensional high definition video system compared to two-dimensional system during single port major lung resection by propensity score matched analysis. Methods: Between March 2012 and December 2015, 213 patients underwent single port thoracoscopic anatomic lung resection for lung malignancy by one surgeon. The patients who underwent wedge resection or converted to open thoracotomy were excluded from analysis. Patient group was divided into two group: two-dimensional (n=95) and three-dimensional group (n=118). Seventy-six patients of each group were matched using propensity score analysis. Results: There were no significant differences in operation time (p=0.44), conversion to open thoracotomy (p=0.088) and postoperative complication (p=0.15) between two- and three-dimensional video system for major lung resection. Subgroup analysis showed that procedure times for lobectomy with segmentectomies (p=0.01), sleeve resection (p=0.64), and additional procedure (p=0.10) were likely to be shorter in three-dimensional group. The number of excised mediastinal lymph nodes was not significantly different (p=0.81). Eye discomfort or headache when using glasses for three-dimensional image was not observed in our study. . Propensity matched analysis.

(See Table next page)
Abstracts

PUB024 REAL-TIME COMPUTED TOMOGRAPHY FLUOROSCOPY GUIDANCE IN A RABBIT MODEL OF SOLITARY LUNG CANCER
Hyun Koo Kim1, Byeong Hyeon Choi2, Hwan Seok Young1, Yu Hua Quan1, Jiyun Rho3, Jae Seon Eo3, Kook Nam Han1, Young Ho Choi1
1Thoracic and Cardiovascular Surgery, Korea University Guro Hospital, Seoul/Korea, Republic of, 2Radiology, Korea University Guro Hospital, Seoul/Korea, Republic of, 3Nuclear Medicine, Korea University Guro Hospital, Seoul/Korea, Republic of

Background:
We evaluate the feasibility and safety of a newly developed solitary lung cancer rabbit model that utilizes real-time computed tomography (CT) fluoroscopy-guided inoculation of VX2 single cell suspensions. Methods: Thirty-eight rabbits were divided into four groups according to number of VX2 tumor cells, Lipiodol amount, Matrigel amount, and injection needle size. The different VX2 tumor cell suspensions were percutaneously injected into rabbits under real-time CT fluoroscopy guidance. Two weeks later, VX2 lung cancers were confirmed by positron emission tomography/CT, necropsy, and histology. Results: Real-time CT fluoroscopy allowed the precise inoculation of tumor cell suspensions containing Lipiodol. Use of Matrigel and a small-sized needle reduced spreading and leakage of tumor cell suspensions in the lung parenchyma. Solitary lung cancers were successfully established in all rabbits in group 4 (22/22, 100%); these rabbits were inoculated with 150 μl VX2 tumor cells filtered through a 100 μm cell strainer, 100 μl Lipiodol, and 150 μl Matrigel, using 26-gauge needles. Pneumothorax was observed in only 2 of 38 rabbits (5.3%).

Conclusion: Real-time CT fluoroscopy-guided inoculation of the appropriate composition of a VX2 tumor cell suspension using a small sized needle is an easy and safe method to model solitary lung cancer in rabbits.

Keywords: Lung cancer animal model, CT guided fluoroscopy

PUB025 COMPARISON OF SURGICAL OUTCOMES BETWEEN MULTIPORT AND SINGLE PORT THORACOSCOPIC LOBECTOMY FOR LUNG CANCER: PROPENSITY SCORE MATCHED ANALYSIS
Hyun Koo Kim, Kook Nam Han, Young Ho Choi
Thoracic and Cardiovascular Surgery, Korea University Guro Hospital, Seoul/Korea, Republic of

Background: We evaluated operative outcomes of single port thoracoscopic lobectomy compared to conventional multiport thoracoscopic lobectomy to determine its safety and oncologic efficacy by propensity score matched analysis. Methods: Between November 2006 and June 2015, retrospective data of 386 patients who underwent thoracoscopic lobectomy for single lobe in non-small cell lung cancer by one surgeon. The cases of sublobar resection and multiple or complex procedures were excluded in this analysis (n=145). Patients were divided into single port group (n=159) and multiport group (n=82). Seventy-six patients of each group were matched using propensity score analysis. Results: The mean operative time in learning period (<50 cases) (185± 63 min in single port vs. 184 ±59 in multiport, p=0.879) and the conversion to open thoracotomy (3 cases in single port and 2 case in multiport, p=0.649) were not different significantly between the two groups. After experiencing of 28 single port lobectomy, there was no conversion to open thoracotomy. The number of excised lymph node was not impaired by single port thoracoscopic lobectomy (17±10 in single port vs. 19±11 in multiport, p=0.512). The survival curve in pathologic stage I population was not different between groups (p=0.969).

Conclusion: Three-dimensional video system is a safe and feasible option for minimally invasive major lung resection for lung cancer and might be helpful in performing thoracoscopic complex procedures, segmentectomy, sleeve resection under single port thoracoscopic surgical field.

Keywords: lung cancer, Thoracoscopic surgery

2D (n=76)  3D (n=76)  P

<table>
<thead>
<tr>
<th></th>
<th>2D</th>
<th>3D</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operation time</td>
<td>180±64</td>
<td>188±57</td>
<td>0.439</td>
</tr>
<tr>
<td>Lobectomy</td>
<td>190±44</td>
<td>182±55</td>
<td>0.093</td>
</tr>
<tr>
<td>Lobectomy + segmentectomy</td>
<td>224±93</td>
<td>193±137</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sleeve resection</td>
<td>173±11</td>
<td>133±31</td>
<td>0.640</td>
</tr>
<tr>
<td>Lobectomy + others</td>
<td>203±66</td>
<td>207±150</td>
<td>0.098</td>
</tr>
<tr>
<td>Number of lymph node excision</td>
<td>18.4±10.5</td>
<td>18±9.3</td>
<td>0.811</td>
</tr>
<tr>
<td>Conversion to open</td>
<td>4</td>
<td>3</td>
<td>0.698</td>
</tr>
</tbody>
</table>

Table. The conditions between expectation on computed tomography (CT) guided inoculation and tumor necrosis.
Abstracts

**PUB027 APPROPRIATE ENDPOINT FOR STAGE I NSCLC: CORRELATIONS OF LONG-TERM SURVIVAL WITH DISEASE-FREE AND RECURRENCE-FREE SURVIVAL**

Kay See Tan1, Takashi Eguchi2, Prasad Adusumilli2
1Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York/NY/United States of America, 2Thoracic Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York/NY/United States of America

**Background:** Overall survival (OS) is commonly reported as an optimal endpoint as it incorporates mortality from the cancer itself, from treatment as well as other causes. We hypothesized that in patients who underwent curative-intent resection for stage I NSCLC, reduced recurrence results in improved OS; recurrence is an appropriate endpoint. We examined the correlations between OS, lung-cancer-specific survival (CSS), disease-free survival (DFS) and recurrence-free survival (RFS).

**Methods:** Retrospective reviews identified 5199 NSCLC patients who underwent curative-intent resection of primary lung cancer between a single institution (Columbia University Medical Center) from 2000-2011. Survival was estimated by the Kaplan-Meier approach. Correlations between pairs of endpoints (ρ) were reported as correlation coefficients from bivariate survival models using 100 iterative multiple imputation. For DFS, recurrence and death without recurrence are both considered events, whereas death without recurrence is censored in RFS. Results: Among 2186 patients, 70.1% were age 65+, 44.3% with ≥2cm tumors. OS and CSS are 78% and 90%, respectively. In the presence of recurrence, DFS and RFS are 70% and 81%, respectively.

**Conclusion:** The correlation between DFS and OS is 0.926 (95% CI, 0.912, 0.937), indicating excellent correlation between the two endpoints, regardless of tumor size. The correlation between recurrence and OS is slightly lower (p=0.812), while the correlation between recurrence and CSS is as high as DFS vs OS (p=0.896). The correlation between DFS and OS did not differ by surgery type; however, in patients without OS or CSS, subgroups had lower correlation. **Conclusion:** Among early stage NSCLC patients receiving surgical interventions, recurrence is an appropriate endpoint with high correlation with long-term outcomes, particularly among older surgeries.

**Keywords:** overall survival, surgical outcomes, clinical endpoints, Long term follow-up

**PUB028 IMPLEMENTATION AND EVALUATION OF A LUNG CANCER MULTIDISCIPLINARY TEAM (MDT) COMMUNICATION TOOL FOR GENERAL PRACTITIONERS (GPs)**

Clare Brown1, Gemma Collett2, David Barnes3, Tim Shaw1, Nicole Rankin4, Philip Beale5, Brian McCaughrn6, Merian Findlay7
1Cardiothoracic, Royal Prince Alfred Hospital, Sydney/ACT/Australia, 2NHMRC Clinical Trials Centre, Sydney Catalyst Translational Cancer Research Centre, Sydney/ACT/Australia, 3Reasearch in Implementation Science and Ehealth (Rise), The University of Sydney, Sydney/NSW/Australia, 4NHMRC Clinical Trials Centre, Sydney Catalyst Translational Cancer Research Centre, Sydney/Australia, 5Cancer Services, Sydney Local Health, Sydney/Australia, 6Cancer Services, Sydney Local Health, Sydney/Australia

**Background:** The Royal Prince Alfred Hospital lung multidisciplinary team (MDT) was established in 1984. Historically, information about MDT decision making was captured as free text in the electronic medical record, including patient investigation and staging. This information was accessible to clinical staff, however, it was not routinely distributed to general practitioners (GPs) involved in the patient’s care. We identified a potential gap in the current reporting and communication processes. **Methods:** The form was revised by the MDT clinicians prior to implementation. Registrars completed the form for all patients presented during the MDT. The form was sent to each patient’s GP within 1-2 days. A brief telephone survey was conducted with consenting GPs within 2 weeks of receipt. Data were collated from the completed surveys. **Results:** To date, 61 GPs have completed phone surveys; 51% were
male; 43% were from regional and 57% metropolitan settings. Nearly all participants (96%) reported that the information provided in the form was useful and relevant; and 87% reported it will be used for coordination and planning of their patient’s treatment pathway. Most (90%) reported receiving the form in a timely manner, and 84% found it easy to interpret and used it in communication with the patient. Conclusion: The evaluation has confirmed that GPs found the form to be delivered in a manner that was timely, acceptable and appropriate. It is anticipated that it will benefit GPs in communicating the outcomes of MDT treatment recommendations to their patients. The template will be translated to other MDTs for different tumour groups.

Keywords: MDT, communication

PUB0209 UNIFORM AND BLIND CAUSE DEATH VERIFICATION OF THE NELSON LUNG CANCER SCREENING PARTICIPANTS
Uraejh Yousaaf Khan,1 Carlijn Van Der Aals1, Joachim Aerts2, Michael Den Bakker1, Harry De Koning1
1Public Health, Erasmus MC - Public Health, Rotterdam/Netherlands, 2Department of Pulmonary Medicine, Amphia Ziekenhuis, Breda/Netherlands, 3Pathology, Maassstad Hospital, Rotterdam/Netherlands.

Background: The primary outcome of the Dutch-Belgian lung cancer screening trial (NELSON) is lung cancer specific mortality. An accurate answer regarding the cause of death (CoD) in the NELSON trial is crucial for assessment of the true screening effect. Death certificates can be inaccurate and therefore a clinical expert of committee (CEC) was formed to review the blinded medical files and to assign CoD. In this study, a selection of the medical files of the deceased lung cancer patients were reviewed and the outcomes were compared with the official death certificates.

Methods: For the review process 274 completed medical files of Dutch deceased participants with lung cancer diagnosis during the course of the study or those with a notation of lung cancer death on the death certificate were selected. Files were blinded for the study arm and patients identity. The CEC was formed by a pulmonologist-oncologist and a pathologist specialized in lung oncology. Both members reviewed all the blinded medical files independently and in a uniform manner. Six outcomes were possible: definitely lung cancer death (LCD), probably LCD, possible LCD, unlikely LCD, intercurrent death with lung cancer as contributing factor or definitely no LCD. The percentage agreement and the Cohen’s kappa statistics between the two CEC members were calculated. In case there was no agreement, the files were discussed by the two CEC members in a consensus meeting. The consensus reached after completing the review process was considered as the gold standard.

Results: Compared to all NELSON participants the reviewed participants were at baseline older (61.0 vs. 58.0 years), less often female (12.4% vs. 16.4%), more often current smokers (66.8% vs. 55.4%) and had smoked more pack-years (43.7 vs. 38.0 years). The overall concordance and the kappa between the CEC members were 85.4% and 0.56 (0.42-0.67, p<0.001), respectively. The sensitivity and specificity of the official death certificate were 92.6% and 98.3%. Conclusion: It is important in lung cancer screening to verify in detail the cause of death, because the official death certificate report may not be accurate. In the NELSON trial, so far, a high overall sensitivity and specificity of the official death certificate was observed. So far, in lung cancer death biases seem small.

Keywords: Mass screening, lung cancer, computed tomography, early detection of cancer

PUB030 USE NSE AND PROGRP TO JUDGE THERAPEUTIC
Di Minervi

Background: Small cell lung cancer (small cell lung cancer, SCLC) accounts for about 13% of lung cancer patients. Compared with non-small cell lung cancer, it has a higher metastatic potential and sensitive to first-line cytotoxic chemotherapy. NSE and ProGRP in SCLC sometimes can be high. Methods: Collect 205 cases of untreated small cell lung cancer (SCLC) 2013-2016 in Peking Union Medical College Hospital, analyze their clinical data. Compare before and after the treatment course, peripheral blood tumor index of neuron specific enolase (NSE) and gastrin release peptide precursor (ProGRP) level and follow-up, through the comparison of the TTP, Cr rate data of NSE and ProGRP level on the treatment and prognosis of guiding significance.

Results: ORR, TTP, and 2 year survival rates were higher in abnormal NSE and ProGRP than in patients with normal NSE and ProGRP in patients with SCLC, but not statistically significant. NSE and ProGRP decreased to normal compared with the normal subjects after 4 chemotherapy, and had statistical significance. Compared to all NELSON participants the reviewed participants were at baseline older (61.0 vs. 58.0 years), less often female (12.4% vs. 16.4%), more often current smokers (66.8% vs. 55.4%) and had smoked more pack-years (43.7 vs. 38.0 years). The overall concordance and the kappa between the CEC members were 85.4% and 0.56 (0.42-0.67, p<0.001), respectively. The sensitivity and specificity of the official death certificate were 92.6% and 98.3%. Conclusion: It is important in lung cancer screening to verify in detail the cause of death, because the official death certificate report may not be accurate. In the NELSON trial, so far, a high overall sensitivity and specificity of the official death certificate was observed. So far, in lung cancer death biases seem small.

Keywords: Mass screening, lung cancer, computed tomography, early detection of cancer

PUB031 PRIMAL: A PHASE 1B STUDY OF PEGPH20 PLUS DOCETAXEL IN PATIENTS WITH PREVIOUSLY TREATED HYALURONAN (HA)-HIGH ADVANCED NSCLC
Megan Baumgart,1 Lyudmila Bazhenova,2 Daniel Haggstrom,2 Joaquina Baranda3, Chandra Belani1
1University of Rochester Medical Center, Rochester/NY/United States of America, 2University of California San Diego, Moores Cancer Center, La Jolla/CA/United States of America, 3Levine Cancer Institute, Carolinas Healthcare System, Charlotte/NC/United States of America, 4Halozyme Therapeutics Inc., San Diego/CA/United States of America, 5Vasona Oncor, TTP, and 2 year survival rates of patients with normal SCLC and ProGRP were higher than those in patients with elevated NSE and ProGRP, and the elevation of and NSE showed poor prognosis. NSE and ProGRP decreased after chemotherapy, which indicated that the prognosis was good, especially the NSE decline was more significant. Therefore, ProGRP and NSE have a certain significance in predicting the prognosis and treatment effect of SCLC, and the significance of NSE is more prominent.

Keywords: ProGRP, NSE, SCLC
unclear due to its heterogeneous population. **Methods:** We retrospectively reviewed clinicopathological factors of 161 patients who underwent surgical resection for radiologically diagnosed CNI NSCLC treated from 2001 to 2013 in our institute. The patients without preoperative aggressive invasive mediastinal evaluation and induction treatment were enrolled. To identify the population who can benefit from invasive mediastinal staging, we analyzed predictive factors of pN2 status. Furthermore, disease free survival (DFS), overall survival (OS) and factors affecting them were also investigated. **Results:** One hundred nineteen patients (73.9%) with pN0-1 and 42 patients (26.1%) of pN2 were identified. More patients of female sex, high serum CEA and adenoscarcinoma (AD) histology were included in the pN2 group (p=0.044, 0.028 and 0.024, respectively). The univariate analyses showed that higher age and AD histology were potential predictor for pN2 status (p=0.048 and 0.01, respectively) and the multivariate analysis demonstrated AD histology was a significant predictor for pN2 status (HR: 2.645, p=0.015). Five-year OS rate of the pN0-1 and pN2 AD patients were 56.8% and 34.0%, respectively (p=0.46). Those of non-AD patients were 70.2% and 64.9%, respectively (p=0.94). In AD patients, five-year DFS rate of the pN0-1 was 50.2%, which was significantly better than that of pN2 patients, 5.8% (p=0.002). While those of non-AD patients were not different, demonstrating 55.4% and 73.9%, respectively (p=0.48). Out of 26 AD patients with pN2 disease, 24 patients (92.3%) experienced recurrence. Twenty-one patients (80.8%) of them were accompanied with non-local disease. **Conclusion:** AD histology was the independent predictor for pN2 status in resected CNI NSCLC. Surgical outcomes of CNI/pN2 AD patients were poor and the efficacies of therapies are limited. The evaluation of invasive modalities may be more beneficial for AD patients in terms of prognostic distinction and decision of treatment strategies.

**Keywords:** CNI NSCLC, mediastinal evaluation, non-adenocarcinoma, Adenocarcinoma

**PUB034 PROFILE OF LUNG CANCER IN DEVELOPING COUNTRY: SINGLE CENTRE EXPERIENCE CHANGING PARADIGM**

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**Background:** Adenocarcinoma is the commonest histological subtype of non-small cell lung cancer (NSCLC) in most of the Western countries. However, in India squamous cell carcinoma has been reported as the commonest histological type in most of the series. The aim of the study is to analyze the clinico-pathological profile, treatment outcome and survival of NSCLC treated at our centre. **Methods:** We analyzed 364 NSCLC registered at our centre over a period of three years. They were evaluated for their clinical and pathological profiles, treatment received and outcome. We also analyzed epidermal growth factor receptor (EGFR) in 250 patients for which formalin-fixed paraffin-embedded tissues was available. EGFR sequencing was performed with ABI PRISM 310 genetic analyzer. **Results:** Median age was 55 years with a male:female ratio of 5:1. Seventy % of patients were smokers. Adenocarcinoma was the commonest histological subtype after the pathology review. Among NSCLC, 75% cases were of stage IV. Forty % of patients had mutation in one of the four exons characterized. Patients whose EGFR mutational status was not available at presentation before the start of treatment were started on chemotherapy. If EGFR mutational analysis was available and mutations were present, the patients were started on either upfront tyrosine kinase inhibitor (TKI), 30% or on chemotherapy arm were allowed to finish six cycles and then start with maintenance TKIs, 40%. The median progression free survival for patients with and without mutations was 12 months and 8 months. A median PFS of 16 months was seen in the mutation-positive group that received both chemotherapy followed by switch maintenance with TKIs versus 9 months in the group that received only TKI. **Conclusion:** This analysis suggests that adenocarcinoma, the commonest histological subtype in India, Most of the patients present at advanced stage and outcome remains poor. The prevalence of EGFR mutations in this population of NSCLC patients was 42 % with exon 19 mutation being the most common.

**Keywords:** lung cancer, Developing Country

**Median Survival Time (Months)**

<table>
<thead>
<tr>
<th>Stage</th>
<th>CR N=23,261 (2.8%)</th>
<th>CS N=26,754 (2.9%)</th>
<th>CR N=245,114 (26.9%)</th>
<th>SURG N=106,719 (11.73%)</th>
<th>CHEMORAD N=132,032 (14.5%)</th>
<th>RAD N=162,555 (17.9%)</th>
<th>SURGRAD N=8,444 (0.9%)</th>
<th>UNK N=14,073 (1.6%)</th>
<th>No TX N=190,539 (21%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>40.1(37.6-42.4)</td>
<td>77.9(74.8-82)</td>
<td>21.0(20.5-21.6)</td>
<td>77.7(73.7-82)</td>
<td>15.4(14.7-16.2)</td>
<td>22.1(21.7-22.4)</td>
<td>34.9 (32.9-36.9)</td>
<td>89.4 (81.3-96.2)</td>
<td>12.7 (12.4-12.9)</td>
</tr>
<tr>
<td>II</td>
<td>35.8(36.4-41.6)</td>
<td>60.1(56.6-63.4)</td>
<td>17.6(17.2-18.0)</td>
<td>36.4(34.7-38.2)</td>
<td>12.7(11.9-13.5)</td>
<td>10.7(10.4-11.1)</td>
<td>22.9 (21.0-24.2)</td>
<td>29.3 (26.2-31.6)</td>
<td>5.9 (5.7-6.3)</td>
</tr>
<tr>
<td>IIIA</td>
<td>32.6(31.6-33.9)</td>
<td>40.8(38.4-42.9)</td>
<td>15.9(15.7-16.0)</td>
<td>25.2(23.5-26.9)</td>
<td>11.6(11.3-11.9)</td>
<td>8.3(8.2-8.5)</td>
<td>19.2 (17.9-21.4)</td>
<td>14.7 (13.4-15.9)</td>
<td>5.0 (4.9-5.2)</td>
</tr>
<tr>
<td>IIIB</td>
<td>27.7(25.2-28.9)</td>
<td>32.4(29.4-35.3)</td>
<td>12.8(12.6-12.9)</td>
<td>23.6(21.2-25.8)</td>
<td>9.7(9.6-9.9)</td>
<td>5.4(5.2-5.5)</td>
<td>14.5 (12.6-15.5)</td>
<td>8.9 (8.3-9.5)</td>
<td>2.3 (2.3-2.4)</td>
</tr>
<tr>
<td>IV</td>
<td>16.5(15.5-17.6)</td>
<td>19.6(18.1-20.8)</td>
<td>7.5(7.4-7.5)</td>
<td>10.2(9.4-11)</td>
<td>8.4(8.4-8.5)</td>
<td>2.8(2.7-2.8)</td>
<td>7.9(7.3-8.4)</td>
<td>5.2 (4.9-5.5)</td>
<td>1.7(1.7-1.7)</td>
</tr>
</tbody>
</table>

Across all stages CRS was used in 2.6% (23,261) and CS was used in 2.9% (26,754) (CRS Stage I – 2.2%, II- 8.7%, IIIA- 7.6%, IIIB- 2.17%, IV- 0.8% and CS Stage I-5.9%, II- 12%, IIIA-3.6%, IIIB- 1.2%, IV- 6%) (Distribution of treatment groups is shown in Table 1). For stage IIIA there was a 0.18% increase in the use of CRS over the study period (p=0.011). For all other stages, there was no significant change in the proportion of patients treated with CRS. The use of CS did significantly increase: stage I (0.5%), II (1.3%), IIIA (0.001), IIIB (0.32%), and IV (p=0.0001). There was no significant change in the use of CS for stage IIIB or IV. Independent of stage, patients treated with CRS or CS had significantly longer OS (p=0.0001) (Table 1). **Conclusion:** Survival in patients treated with CRS or CS is superior to other treatment modalities across all stages, but the use of CRS and CS is low when compared to other modalities. Future studies need to determine why multimodality treatments including CRS and CS are used so sparingly despite the recognized survival benefit.

**Keywords:** Multimodality treatment, survival, treatment patterns
**PUB035 FEASIBILITY OF STEREOTACTIC ABLATIVE RADIOTHERAPY (SABR) FOR LOCALLY-ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC)**

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**Background:** SABR has decreased the proportion of elderly patients with early stage NSCLC who go untreated and as a result population-based survival has improved. As locally-advanced NSCLC is more common and standard-of-care chemoradiotherapy more toxic, the public health impact of patients with advanced disease going untreated is likely greater than those diagnosed early. We assessed the feasibility of SABR for locally-advanced NSCLC. **Methods:** Seventeen patients with N2 and/or N3 locally-advanced lung cancer were retrospectively replanned. Targets and organs-at-risk (OAR) were delineated using 4DCT and replanned with RapidArc delivery (AcurosXB V13.6). Three planning approaches were assessed; conventional approach (1.0cm ITV to PTV expansion, prescribed to 100%); SABR approach (0.5cm ITV to PTV expansion, prescribed to 80%) and a hybrid approach (0.5cm ITV to PTV expansion, prescribed to 100%). We assessed the feasibility of three dose regimes, with PTVs doses all having a biologic equivalent of 60Gy in 30 fractions (β=10). The planning aim was to determine the least number of fractions delivered that achieved >95% target coverage by >95% dose while maintaining all OAR tolerances. Descriptive statistics were used.

<table>
<thead>
<tr>
<th>OAR dose constraints (Gy) per dose regime</th>
<th>PTV Prescription</th>
</tr>
</thead>
<tbody>
<tr>
<td>4Gy in 5 fractions</td>
<td>Target volume</td>
</tr>
<tr>
<td>4Gy in 8 fractions</td>
<td>50.4Gy in 12 fractions</td>
</tr>
<tr>
<td>Heart</td>
<td>38</td>
</tr>
<tr>
<td>Trachea/Bronchi</td>
<td>36</td>
</tr>
<tr>
<td>Oesophagus</td>
<td>35</td>
</tr>
<tr>
<td>Spinal Canal</td>
<td>28</td>
</tr>
</tbody>
</table>

**Results:** Twelve patients had N2 involvement whilst five had N3 involvement. Mean ITV size was 203.9cc (range 71.06-11c). The hybrid approach generated acceptable plans in 44% of patients (7/17), while the conventional and SABR approaches achieved 18% (3/17) and 6% (1/17) respectively. If acceptable plans in 41% of patients (7/17), while the conventional and SABR approaches in 6% (1/17) of patients. Further studies included larger numbers of patients are expected to validate such a finding and explore whether SABR may be feasible for locally-advanced NSCLC and requires using a hybrid approach to show potential of feasibility. The clinical compromises required to increase its utility may be acceptable in certain scenarios.

**Keywords:** Stereotactic ablative radiotherapy, locally-advanced non-small cell lung cancer, elderly, Radiotherapy planning

**PUB035 PROGNOSTIC SIGNIFICANCE OF CANCER STEM CELL MARKERS CD44 AND ALDH1 EXPRESSION IN ADENOCARCINOMA OF THE LUNG**

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**Background:** Adenocarcinoma is the most common histologic type of non-small cell lung carcinomas. The existence and role of lung cancer stem cells (CSCs) in human tissue is controversial. The aim of this study is to investigate the expression of CD44 and ALDH1 and evaluate their relationships with clinicopathologic parameters including recurrence. **Methods:** Immunohistochemistry for CD44 and ALDH1 was performed in 77 curative surgical resection cases with primary lung adenocarcinoma using tissue microarrays. **Results:** High expression of CD44 and ALDH1 were found in 64.9% and 33.8% in the study group, respectively. High CD44 expression was statistically associated with female gender (p=0.010), no preauricular (p=0.017), and smaller tumor size (p=0.043). High ALDH1 expression was statistically associated with female gender (p=0.003), NO LN (p=0.006), low pathologic stage (p=0.019), and smaller tumor size (p=0.011). The high expression of CD44 and ALDH1 showed lower recurrence compared with the low expression (p=0.014, p=0.023). In multivariate analysis, high expression of CD44 and early pathologic stage were the independent favorable prognostic factors for recurrence. **Conclusion:** Our results showed that the expression of CSCs was associated with a good prognosis. There is a need for more research about CSCs in human lung adenocarcinoma.

**Keywords:** Cancer Stem Cells, recurrence, NSCLC adenocarcinoma

**PUB037 COMPUTED TOMOGRAPHY NUMBER CHANGES OF GROSS TUMOR VOLUME WITH MVCT SCANS IN TOMOTHERAPY MAY EARLY DETECT THE RADIOSENSITIVITY OF NSCLC PATIENTS**

**Nasha Zhang, Zhenxuan Wu, Hui Zhu, Wang Jing, Jiming Yu**

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**Background:** Evidences have showed that the CT number (CTN) for tumor and certain normal tissues can change after irradiation, and the CTN change may be an early indicator for radiosensitivity of NSCLC patients. **Methods:** Patients with stage I to III non-small cell lung cancer were eligible in this prospective study. MVCT scans were acquired during tomotherapy. The distribution of CTN and the corresponding CTN values from the first treatment to the 15th treatment were collected based on the GTV generated on daily MVCT. The dose-response curve for decreased CTN of patients was quantified using the slope of a linear regression. The CTN decreased per Gy (ΔHU/Gy) for each patient was calculated and a cut-off value was taken after the whole radiation therapy completed, based on which the post-treatment tumor responses were assessed by two thoracic radiologists. According to the tumor responses, a cut-off value for ΔHU/Gy was calculated by SPSS software. **Results:** From Jun. 2015 to Dec. 2015, 32 eligible patients were enrolled in this study. Males: 19 (60%), Females: 13 (40%), median age: 61.7 years (range 43.3-70.9). The median radiation dose was 60Gy (range 54-63Gy). In the whole group, the mean CTN was decreased by 37.35 ± 27.07 HU from the first treatment to the 15th treatment. The mean GTV was reduced by 10.26 ± 10.15 cm³. The CTN decreased per Gy (ΔHU/Gy) was ranged from 0.37 to 2.37 among all patients. Seven patients (21.9%) reached CR, 18 patients (56.2%) reached PR, and 7 patients (21.9%) reached SD after the complete tomotherapy. The mean CTN reduction ranged from 28.1H to 64.0 HU in patients whose post-treatment tumor responses were CR or PR and the CTN changes were linearly correlated with the radiation dose (R²=0.87, p<0.001). The mean CTN changes in the left 17 patients were ranged from 9.2 HU to 26.2 HU. The cut off value for ΔHU/Gy was 0.97, above which patients could have a better radiosensitivity and a further favorable post-treatment tumor response. **Conclusion:** On an early and quantitative scale, the CTN changes of MVCT in tomotherapy may early detect the radiosensitivity of NSCLC patients. Further studies include larger numbers of patients are expected to validate such a finding and explore whether CTN changes of MVCT hold the potential to optimize treatment by adjusting radiation intensity or modifying the therapeutic regimen, based on the observed radiosensitivity of patients. **Keywords:** computed tomography number changes, gross tumor volume, radiosensitivity, MVCT scans in Tomotherapy

**PUB038 A MULTIMEDIA SELF-MANAGEMENT INTERVENTION TO PREPARE PATIENTS AND FAMILY CAREGIVERS FOR LUNG SURGERY**

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**Background:** Due to healthcare environment changes and advances in surgical care, patients are discharged from the hospital earlier and earlier following lung surgery. Patients often feel significant postoperative care and the greater proportion of the caregiving burden has fallen on family caregivers (FCGs). There are few evidence-based, dyadic interventions developed specifically for lung surgery patients and FCGs. In this study, we tested the feasibility and acceptability of a multimedia self-management intervention to prepare patients and their FCGs for lung surgery. **Methods:** Patients and their FCGs were sequentially enrolled into a usual care group or an intervention group, which received the multimedia (15 minute video and print material) intervention, Preparing For Your Lung Surgery. Intervention content development was guided by the chronic care self-management model (CCM). The intervention was delivered in two doses: before surgery and before hospital discharge. Patient and FCG outcomes were assessed at baseline (before surgery), before hospital discharge and at 4 weeks post-discharge. Intervention usability and acceptability data were obtained from both patients and FCGs. **Results:** A total of 53 patients/FCGs were enrolled in the study (23 usual care, 30 intervention). We observed little difference in all outcome scores for the usual care group from pre-to post intervention. A significant, clinically meaningful improvement in emotional well-being subscale score was seen in the intervention group from pre-to post.
Abstracts

Post-intervention (16.0 versus 20.0, p = 0.005). Patient activation (confidence in managing overall healthcare) for the intervention group improved from pre- to post-intervention (71.0 versus 75.5). Intervention group patients had more confidence in self-care at hospital discharge (20.5 versus 18.9). Intervention group FGs reported less objective caregiving burden (extent to which care responsibilities are viewed as disruptive) at hospital discharge (13.4 versus 16.2). Statistically significant improvements in recovery-related knowledge scores from pre-to post-intervention were observed for both patients (8.8 versus 9.0, p = 0.001) and FGs (8.8 versus 9.6, p = 0.02) in the intervention group. Mean length of hospital stay was 4.1 for usual care and 3.2 for intervention group. Intervention usability and acceptability scores were high (3.7/4.0 for patients, 3.6/4.0 for FGs).

Conclusion: A multimedia self-management intervention that begins before surgery was feasible and acceptable in preparing patients and FGs for lung surgery. A randomized trial is needed to test the efficacy of the intervention on patient/FG outcomes and healthcare resource use.

Keywords: family caregivers, quality of life, Thoracic Surgery

PUB039 ROLE OF PEMETREXED AND CISPLATIN COMBINATION THERAPY IN ADVANCED NON-SQUAMOUS CELL LUNG CANCER

Manoj Behera, Faiz Ansari, Samrat Dutta

1Clinical Oncology, AllAMS Ahce, Cuttack/India, 2Radiation Onc, Sm Hospital, Delhi/India, 3Oncology, Nbm College, Siligud/India

Background: NSCLC is the leading cause of cancer death in today's scenario. Despite significant progress in early stage disease, survival rates for advanced disease remain low. Platinum doublet chemotherapy has become the current standard of care for advanced nonsmall cell lung cancer (NSCLC) which has shown modest prolongation of survival and improvement in cancer-related symptoms.

Methods: All the patients received Pemetrexed® 500mg/m2 Day 1 and Cisplatin® 75mg/m2 every 21 days with restaging after 3 and 6 cycles. Overall response rate was the primary end point and PFS as secondary end point.

Results: In this retrospective study, 90 patients were analyzed. The patients treated with pemetrexed plus cisplatin had a median age of 58 years and were predominantly men (70) with nonsquamous histology (60), stage IV (52) disease, and a performance status of 0 (60). Response rates were 48%. Median time to progression was 7 months. Median overall survival was 12 months. The 1year survival rate was 52%

Conclusion: The combination of pemetrexed and cisplatin was effective and safe and were predominantly men (70) with nonsquamous histology (60), stage IV (52) disease, and a performance status of 0 (60). Response rates were 48%. Median time to progression was 7 months. Median overall survival was 12 months. The 1year survival rate was 52%.

Keywords: NSCLC, chemotherapy, Radiotherapy

PUB040 TREATMENT RESPONSE AND PROPHYLACTIC CRANIAL IRRADIATION ARE IMPORTANT PROGNOSTIC FACTORS IN LD SCLC PATIENTS STAGED WITH CMR.I

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1Department of Radiation Oncology, Ludwig-Maximilians-University Munich, Munich/Germany, 2Department of Radiation Oncology, University of Rostock, Rostock/Germany, 3Department of Radiation Oncology, Friedrich Alexander University Erlangen-Nuremberg, Erlangen/Germany

Background: The role of prophylactic cranial irradiation (PCI) in LD SCLC has proven to significantly decrease the incidence of brain metastases (BMs) with only modest improvement of survival. Methods: To evaluate an exact impact of PCI, we reviewed 184 LD SCLC patients treated with definitive chemoradiotherapy (CRT). PCI was applied in the partial and complete responders exclusively when contrast enhanced cranial magnetic resonance imaging (cMRI) before and after primary treatment showed no BMs. Correlation between application of PCI and time to progression (TTP) as well as overall survival (OS) was analysed. Kaplan-Meier analysis and Cox regression were used to describe survival within subgroups defined by application of PCI.

Results: Concurrent and sequential CRT was applied in 71 (39%) and 113 (61%) patients, respectively. Metachronous BMs were detected in 58 (32%) patients. PCI was applied in 71 (39%) partial and complete responders. 15 (21%) patients developed BMs after PCI. Median TTP and OS in the therapy responders treated with PCI were 29 and 28.6 compared to 12.7 (range: 10.1-16.3) (p = 0.0001) and 13.8 (range: 11.4 – 16.3) (p < 0.0001) months in the rest of patient cohort, respectively. The effect of PCI was independent of gender. In the multivariate analysis, application of PCI in responders was a variable that significantly correlated with TTP (HR 2.16 CI HR 1.37-3.42, p = 0.001) and OS (HR 1.89 CI 1.37-2.63, p < 0.0001) after adjustment for other patient- and treatment-related prognostic factors.

Conclusion: In LD SCLC patients comprehensively staged with cMRI and treated with CRT, treatment response and application of PCI strongly correlated with prolonged TTP and OS.

Keywords: limited disease small cell lung cancer, Chemoradiotherapy, lung cancer, prophylactic cranial irradiation

PUB041 HGF, VEGFA AND ANGPT2 PREDICT CLINICAL BENEFIT FROM BEVACIZUMAB AND CHEMOTHERAPY IN PATIENTS WITH ADVANCED NSCLC (SAKK19/09)

Sacha Rothschild1, Oliver Gautschi2, Nathalie Schuster1, Qiuyi Li, Spasenija Ochsenbein1, Richard Cathomas1, Daniel Rauch1, Milkos Piess1, Adrian Ochsenbein2, Rolf Stahl1

1Medical Oncology, University Hospital Basel, Basel/Switzerland, 2Medical Oncology, Lucerne Cantonal Hospital, Luzern/Switzerland

Background: Bevacizumab (Bev) is a monoclonal antibody against the vascular endothelial growth factor. No predictive biomarkers for the use of Bev have been established so far. We aim to find out the candidates of predictive genes for progression-free survival (PFS) and overall survival (OS) using baseline tumor samples of patients treated in the trial SAKK19/09 (NCT0116219).

Methods: SAKK19/09 was a non-randomized phase II trial with two sequential cohorts including patients with non-squamous NSCLC and EGFR wild-type. In Cohort 1, 77 patients were treated with 4 cycles of cisplatin (C) 75mg/m², pemetrexed (Pem) 500mg/m² and Bev 7.5mg/kg, followed by Bev/Pem maintenance. Cohort 2 included 52 patients treated with C/Pem followed by Pem maintenance. RNA was isolated from tumor tissue sections and processed for gene expression analysis by NanoString. Expression values were normalized using 4 control genes. For each gene, treatment and the interaction of these two, a Cox regression was performed with normalized expression divided by its interquartile range for PFS and OS using baseline tumor samples of patients treated in the trial SAKK19/09 (NCT0116219).

Results: We analyzed 109 patient samples (63 in Cohort 1; 46 in Cohort 2) with 201 genes assessed at baseline. We found 6 genes potentially predicting PFS (BTLA, CD25A, FLT1, MSH4, RPA3, TCF7). Regarding to OS we found a significant effect of interaction for 3 angiogenesis-related genes (ANGPT2, HGF, VEGFA) and 12 other genes (Table 1). Several of these 12 genes (AURKB,
CDC25A, CDC34, CDC6, ERCC6/8, RPA3 have previously been shown to play an important role in DNA repair and cell cycle regulation supporting the hypothesis that Bev improves chemotherapy activity. Additionally, ANGPT2, HGF and VEGFA directly involved in angiogenesis are also predictive. Conclusion: We identified several potentially predictive genes for Bev activity in combination with chemotherapy. Further work is ongoing to explore changes in gene expression using tumor rebiopsies at progression.

Keywords: VEGFA, HGF, Gene Expression, bevacizumab

**PUB042 TUMOR RESPONSE ASSESSMENT BY THE SINGLE-LESION MEASUREMENT PER ORGAN IN SMALL CELL LUNG CANCER**

Jung Han Kim

Oncoology, Internal Medicine, Hallym University Medical Center, Seoul/Korea, Republic of

**Background:** The criterion of two target lesions per organ in the RECIST version 1.1 is an arbitrary one, being supported by no objective evidence. The optimal number of target lesions per organ still needs to be investigated. We compared tumor responses using the RECIST 1.1 (measuring two target lesions per organ) and modified RECIST 1.1 (measuring the single largest lesion in each organ) in patients with small cell lung cancer (SCLC).

**Methods:** We reviewed medical records of patients with SCLC who received first-line treatment between January 2004 and December 2015 and compared tumor responses according to the two criteria using computed tomography. Results: There were a total of 34 patients who had at least two target lesions in any organ according to the RECIST 1.1 during the study period. The differences in the percentage changes of the sum of tumor measurements between RECIST 1.1 and modified RECIST 1.1 were all within 13%. Seventy patients showed complete response and fourteen showed partial response according to the RECIST 1.1. The overall response rate was 61.8%. When assessing with the modified RECIST 1.1 instead of the RECIST 1.1, tumor responses showed perfect concordance between the two criteria (k=1.0).

**Conclusion:** The modified RECIST 1.1 showed perfect agreement with the original RECIST 1.1 in the assessment of tumor response of SCLC. Our result suggests that it may be enough to measure the single largest target lesion per organ for evaluating tumor response.

**Keywords:** Tumor response, RECIST 1.1, modified RECIST 1.1

**PUB043 KIR 2D (L1, L3, L4, S4) AND KIR 3DL1 PROTEIN EXPRESSION IN NON-SMALL CELL LUNG CANCER**

Yayi He1, Paul Bunn, Jr.2, Caicun Zhou3, Daniel Chan4

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**Background:** The expression of KIR 2D (L1, L3, L4, S4) (BC032422/BC032421) and KIR 3DL1 protein expression was evaluated by IHC, and TIL abundance was scored, in 132 surgically resected specimens from patients with NSCLC.

**Results:** Protein expression was positive for KIR 2D (L1, L3, L4, S4) on tumor cells and tumor infiltrating lymphocytes (TILs). Fourteen samples (16.1%) had positive expression on tumor cells and 58 patient samples (43.9%) stained positive for KIR 2D (L1, L3, L4, S4) on the tumor cells, and 10 (16.1%) had positive expression on the TILs. Thirty-three samples (53.2%) expressed positive for KIR 3DL1 on the tumor cells and 31 (50.0%) had positive expression on the TILs. Patients with negative KIR 2D (L1, L3, L4, S4) expression on tumor cells or TILs had longer overall survival (OS) than patients who are KIR 2D (L1, L3, L4, S4) positive on tumor cells (40.70 weeks, 95% CI 24.76-56.65 vs. 7.10 weeks, 95% CI 0.00-19.38, P<0.001) or TILs (60.70 weeks, 95% CI 0.00-57.35 vs. 3.90 weeks, 95% CI 0.00-9.17, P<0.001) Likewise, longer OS was significantly correlated with negative expression of KIR 3DL1 on tumor cells (62.30 weeks, 95% CI 0.00-177.37 vs. 13.10 weeks, 95% CI 3.42-22.78, P<0.001) or TILs (62.30 weeks, 95% CI 0.00-152.05 vs. 12.10 weeks, 95% CI 2.61-21.59, P<0.001). Cox regression analysis showed that KIR 2D (L1, L3, L4, S4) on TILs was correlated with OS (P=0.032, Odds Ratio 2.628 95%CI 1.089-6.340).

**Conclusion:** KIR 2D (L1, L3, L4, S4) and KIR 3DL1 expression was correlated with poor prognosis in NSCLC patients.

**Keywords:** KIR 2D (L1, L3, L4, S4), KIR 3DL1, NSCLC

**Figure 1.** IHC staining for KIR 2D (L1, L3, L4, S4) and KIR 3DL1 in NSCLC

**PUB044 TIM-3 PROTEIN EXPRESSION IN NON-SMALL CELL LUNG CANCER AND ITS RELATIONSHIP WITH PD-1/PD-L1 AND TUMOR-INFILTRATING LYMPHOCYTES**

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**Background:** Immunotherapy targeting the programmed death-1 (PD-1)/ programmed death ligand-1 (PD-L1) checkpoint has shown promising efficacy in patients with non-small cell lung cancer (NSCLC). T-cell immunoglobulin domain and mucin domain-3 (TIM-3) is another important checkpoint, and its role in NSCLC is still not clear. In this study, we investigated TIM-3 protein expression and its correlation with PD-1, PD-L1, tumor-infiltrating lymphocytes (TILs), and association with survival in NSCLC.

**Methods:** TIM-3 (DSDSR, Cell signaling), PD-1 (NAT 105, Cell marque) and PD-L1 (22C3, Dako) protein expression was evaluated by IHC, and TIL abundance was scored, in 132 surgically resected specimens from patients with NSCLC.

**Results:** TIM-3 was expressed on the TILs in 18 (13.6%) patients. S8 patient samples (63.9%) were positive for PD-1 on the TILs, and 23 (17.4%) were positive for PD-L1 on tumor cells. Neither TIM-3 nor PD-1 was expressed on the tumor cells. TIM-3 was over expressed on the TILs in adenocarcinoma compared to non-adenocarcinoma (P=0.011). TIM-3 expression on TILs was significantly correlated to that of PD-1 on TILs (P=0.011). In our study, there was no significant difference in recurrence-free survival (RFS) and overall survival (OS) between TIM-3 positive and negative.

**Conclusion:** TIM-3 expresses on TILs in tumor tissues of some NSCLC patients. Its expression was higher in adenocarcinoma and was correlated with PD-1.

**Keywords:** PD-L1, non-small cell lung cancer (NSCLC), PD-1, TIM-3

**Figure 1.** IHC staining for TIM-3 in NSCLC

**Abstracts**

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**Keywords:** VEGFA, HGF, Gene Expression, bevacizumab

**Keywords:** TIM-3 expresses on TILs in tumor tissues of some NSCLC patients. Its expression was higher in adenocarcinoma and was correlated with PD-1.

**Keywords:** PD-L1, non-small cell lung cancer (NSCLC), PD-1, TIM-3

**Keywords:** VEGFA, HGF, Gene Expression, bevacizumab

**Abstracts**

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PUB045 THE CAPABILITY AND CHARACTERISTIC OF HELICAL TOMOTHERAPY AT SPARING HIPPOCAMPUS IN PROPHYLACTIC CRANIAL IRRADIATION

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Background: Prophylactic cranial irradiation (PCI) is efficient at avoiding lung cancer intra-cranial metastasis. However, PCI may cause neurocognitive impairment because of the hippocampal toxicities. It is reported that hippocampus V7.3Gy > 40% is associated with long-term impairment. Considering helical tomotherapy (HT) has higher modulation capabilities, we investigated the capability and characteristic of HT at sparing hippocampus in PCI. Methods: Six anonymous patients previously treated with whole-brain radiotherapy with hippocampal sparing were reviewed. Under 1T-weighted MRI, the hippocampus was contoured, and hippocampal avoidance regions (HAR) were created using a 5-mm volumetric expansion around the hippocampus. The prescription dose 3.0Gy * 10 fractions was assigned on planning target volume (PTV) which was defined as whole-brain minus HAR and bilateral hippocampus. During the HT plan optimization process, evaluation factors of PTV and other dosimetry factors were recorded whenever the mean dose of hippocampus decreased by every 2Gy. Results: The average of six HT plans without hippocampus sparing constraints are as follow: hippo_Dmean 27.33±2.22Gy, HAR_Dmean 28.62±1.84Gy, PTV_Dmean 30.77±0.76Gy, PTV_D2% 30.93±0.61Gy, PTV_D98% 29.86±0.34Gy, PTV_V30Gy 0.97±0.02% and conformal index (CI) 0.85±0.03, homogeneity index (HI) 0.04±0.01, plan delivery duration 13.70±1.92min. When V7.3Gy of bilateral hippocampus achieved 40%, the average dosimetry factors are as follow: hippo_Dmean 8.26±0.24Gy, HAR_Dmean 12.88±1.27Gy, PTV_Dmean 31.00±0.47Gy, PTV_D2% 31.97±0.63Gy, PTV_D98% 21.74±5.44Gy, PTV_V30Gy 0.04±0.01, CI 0.77±0.08, HI 0.35±0.20, plan delivery duration 21.30±4.97min. Conclusion: During the process of hippocampus sparing, HAR_Dmean decreased linearly as well. However, dosimetry variation of PTV presented severely in the falling region. Plan delivery duration was significantly prolonged from (13min to 23 min).

Keywords: prophylactic cranial irradiation, intensity modulated radiotherapy, hippocampus, Helical Tomotherapy

PUB046 THE EFFECT OF TOMOTHERAPY MVCT DIFFERENT SCAN OPTIONS ON IGRT AND ART ACCURACY

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Background: To quantitatively analyze the effect of TomoTherapy MVCT different scan options on IGRT (Image Guided Radiotherapy) and ART (Adaptive Radiotherapy) accuracy. Methods: The CT simulator images of CIRS-002LFC chest phantom and CIRS-002PRA pelvic phantom were scanned and transferred to TomoTherapy TPS. The spine and soft tissue were contoured as virtual whole spine and prostate cancer irradiation plans on each CT sets respectively. There options of Acquisition Pitch (fine, normal, coarse) and the corresponding two options of Reconstruction Interval for each Acquisition Pitch (fine: 1mm or 2mm, normal: 2mm or 4mm, coarse: 3mm or 6mm) were used respectively. From the pelvic phantom, the bigger registration errors (DTA (x^2+y^2+z^2)) were observed on noise and CT values. Results: From MVCT image sets of chest and pelvic phantoms, there’s no significant difference from different Acquisition Pitch and Reconstruction Interval options on adaptive dose calculation (shown in Fig.2). From the chest phantom, the bigger registration errors (DTA=|x+2y+2z|) was used to evaluate the registration errors where x, y, z stands for the registration errors on each (x: lateral, y: longitude, z: vertical) directions. Finally, the Tomo cheese phantom was scanned with three Acquisition Pitch options and the MVCT images were analyzed on noise and CT values. Results: For MVCT image sets of chest phantom, there’s no significant difference from different Acquisition Pitch options on image noise and CT values (shown in Fig.1). For MVCT image sets of chest and pelvic phantoms, there’s no significant difference from different Acquisition Pitch and Reconstruction Interval options on adaptive dose calculation (shown in Fig.2). From the chest phantom, the bigger registration errors (DTA) came from normal-4mm, coarse-3mm and coarse-6mm options and appeared mainly in longitude direction. From the pelvic phantom, the bigger registration errors came from coarse-3mm and coarse-6mm options and appeared mainly in longitude direction too. With the same Acquisition Pitch and Reconstruction Interval options, the ‘Bone and Tissue Technique’ registration option gave bigger errors while ‘Full Image Technique’ gave the smallest errors. Conclusion: The different scan options will not affect the dose calculation accuracy on MVCT. Therefore, the faster scan mode (coarse+6mm) is recommended for ART plan evaluation. While in position correction of IGRT, normal+2mm option is recommended and the ‘Full Image Technique’ may improve the registration accuracy. Manual registration correction is necessary after automatic registrations.

Keywords: Helical Tomotherapy, Megavoltage CT, Image Guided Radiotherapy, adaptive radiotherapy

PUB047 SATB2 EXPRESSION IN LUG ADENOCARCINOMA

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Abstracts Journal of Thoracic Oncology • Volume 12 Issue S1 January 2017
Background: A subset (10-12%) of lung adenocarcinomas may express the gastrointestinal marker CDX-2 making the distinction between metastatic colorectal adenocarcinomas and primary lung adenocarcinoma difficult. Special AT-rich sequence-binding protein 2 (SATB2) was recently identified as a highly specific marker of the glandular epithelium lining the lower GI tract. SATB2 expression is retained in the large majority of colorectal adenocarcinomas (BS-97%) and is only uncommonly expressed in esophageal (6.7%), gastric (0%) and pancreas (4.2%) adenocarcinomas. There is only very limited data available regarding SATB2 expression in lung adenocarcinomas. Here we report our findings on SATB2 expression in 92 cases of lung adenocarcinomas lacking intestinal differentiation and with known CDX-2 expression status. Methods: Four (4) micron sections of previously constructed tissue microarrays (TMA) containing 92 cases of lung adenocarcinomas were subjected to immunohistochemistry for TTF-1, Napsin A, p40, CDX-2 and SATB2 using an autostainer and commercially available monoclonal antibodies. Tumors showing staining of any intensity (for SATB2 and CDX-2) in greater than 5% of the tumor cells were accepted as positive. Results: The cohort consisted of 13 well, 32 moderately and 27 poorly differentiated adenocarcinomas. Eighty-one tumor was positive for at least one adenocarcinoma marker with 68 tumors showing staining for both TTF-1 and napsin A, while p40 was negative in all cases. Positive CDX-2 staining was seen in 9 tumors (10%), while positive SATB2 staining was seen in only one tumor (1%). Focal (≤5%) SATB2 staining was noted in 3 additional tumors. Conclusion: SATB2 is a novel marker that is highly specific for colorectal adenocarcinomas and appears to be rarely expressed in primary lung adenocarcinoma. On the other hand, CDX-2, a widely used marker of gastrointestinal adenocarcinoma is expressed in a subset of primary lung cancers (the current study) making the distinction between primary lung adenocarcinoma and metastatic colorectal adenocarcinoma difficult, especially in small biopsies where we rely more on immunohistochemistry to render a more specific diagnosis. SATB2 appears to be a promising marker that is superior to CDX-2 for distinguishing between primary lung adenocarcinoma and tumors of the lower gastrointestinal tract.

Keywords: Adenocarcinoma, Immunohistochemistry, SATB2, CDX-2

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**Table 2. Summary of autopsy findings**

<table>
<thead>
<tr>
<th>Case</th>
<th>Tumor</th>
<th>TIL</th>
<th>LVI</th>
<th>DAD</th>
<th>Pneumonia</th>
<th>Tumor necrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>ACA in 5 lobes</td>
<td>1+</td>
<td>Yes*</td>
<td></td>
<td>Focal</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>MM in LLL, LUL</td>
<td>3+</td>
<td>No</td>
<td>Focal</td>
<td>RLL</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>ACA in 4 lobes</td>
<td>1+</td>
<td>Yes</td>
<td>LUL, RUL, LLL</td>
<td>LLL RLL LUL</td>
<td>None</td>
</tr>
<tr>
<td>4</td>
<td>MM in 4 lobes</td>
<td>1+</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>None</td>
</tr>
<tr>
<td>5</td>
<td>MM in RUL</td>
<td>1+</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>None</td>
</tr>
<tr>
<td>6</td>
<td>SCC in RLL, LLL, LUL</td>
<td>2+ Yes</td>
<td>RUL, RML, RLL</td>
<td>No</td>
<td>10% and fibrosis</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>SCC in 5 lobes</td>
<td>1+</td>
<td>Yes</td>
<td>LUL</td>
<td>LLL</td>
<td>No</td>
</tr>
</tbody>
</table>

A.C.A. adenocarcinoma; MM: Malignant melanoma; SCC: squamous cell carcinoma; *extensive LVI

**Conclusion:** The majority of patients with clinical diagnosis of pneumonitis did have DAD at autopsy and variable amount of viable tumor in the lungs and at least a few tumor infiltrating lymphocytes. Additional studies are pending the further characterize the phenotype of the TIL and to determine PDL1 and PD1 expression on the tumor cells.

Keywords: Autopsy, lung pathology, Therapy, Immune checkpoint
be a consequence of mutations in cancer associated genes. Some of the most common types of mutations in lung cancer are EGFR, TP53 and KRAS mutations, known to influence treatment response. The purpose of this study was to identify changes associated with smoking status and EGFR, TP53 and KRAS mutations in lung cancer biopsies which may serve as novel targets to overcome treatment resistance. **Methods:** We have performed a profiling of 300 cancer relevant proteins, of which 60 were in a phosphorylated state, using reverse phase protein arrays (RPRA). We analyzed biopsies from 80 non small-cell lung cancer biopsies and correlated the expression pattern with mutation status of EGFR, TP53 and KRAS, in addition to smoking status. The protein expression was correlated with mRNA expression analyzed on hybridization arrays. **Results:** Ten of the samples were EGFR mutated, 9 were never-smokers, 31 TP53 mutated and 32 KRAS mutated. With a FDR < 0.001, we detected 7 proteins (ATPSA, EIF4EBP1, CCNB1, CDK1, CASP3, FNI and CDKN2A) differentially expressed between TP53 mutated and wild type samples. Further, 4 proteins (RPS6K, CAV1, YBX1 and VIM) were higher expressed in KRAS mutated samples compared with KRAS wild type samples. For EGFR mutated samples, only the protein EGFR was upregulated. Three protein were overexpressed in never smokers (EGFR, KRT19 and TUBA1A). A significant correlation between protein expression and mRNA expression were found for all the proteins except YBX1, ATPSA and TUBA1A (p<0.05). These results demonstrate that key driver mutations in lung cancer affect several proteins linked to the same pathway. We observed a significant upregulation of the TP53 cell cycle target genes CDK1 and CCNB1 in samples with TP53 mutations. **Conclusion:** KRAS mutated samples showed an overexpression of cavolin 1 (CAV1), an important regulator of cell proliferation and metastasis, and an increased expression of the mesenchymal protein vimentin (VIM). **Conclusion:** As of today, we do not identify KRAS- and TP53-mutated tumors. However, proteins associated with the mutation status may be new potential therapeutic targets to circumvent treatment resistance. In the present study, we identified both known and novel proteins associated with TP53 and KRAS mutated samples.

**Keywords:** NSCLC, protein expression, TP53, KRAS

**PUB054 COMPREHENSIVE ANALYSIS OF CHROMOSOMAL ALTERATIONS INVOLVING CDKN2A AND 22Q IN MALIGNANT PLEURAL MESOTHELIOMA**

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**Background:** The promise of personalized genomic medicine relies on the identification and clinical management of patients on the basis of specific genomic alterations that drive clinically heterogeneous malignancies. While recent large cohort studies of malignant pleural mesothelioma (MPM) tumors have confirmed that CDKN2A and NF2 are among the most commonly mutated genes, the clinical and biological significance of these molecular alterations remains incompletely characterized. Herein, we explore whether loss of CDKN2A and/or 22q define molecular subclasses in a large cohort of MPM patients. **Methods:** FISH analysis was performed using the Vysis LSIp23/CEP9 Dual Color Probe Set (Abbott Molecular, Des Plaines, IL) for the p16 locus at 9p21, CEP9 at the chromosome 9 centromeric region, and Vysis TUPLE/LSI ARSA Dual color probe Set (Abbott) for TUPLE at 22q11.2, and ARSA at 22q3. At least 50 nuclei were observed per tumor. Aberrations observed in ≥ 2% of nuclei was considered abnormal, based on normal mesothelial cell controls. Loss of CDKN2A or 22q was explored in relation to diagnostic subtype and clinical factors using the Fisher’s exact test. Overall survival (OS) was estimated using the Kaplan–Meier method and compared between groups using the logrank test. **Results:** CDKN2A and 22q FISH data along with patient’s clinical information were collected from 592 MPM patients. Loss of CDKN2A was detected in 329 (56%), and of 22q in 22q (25%) patients. CDKN2A loss was significantly more common among men (p=0.0027) compared to women, and among men older than 60 compared to younger men (p=0.0005). Loss of CDKN2A was also significantly correlated with self-reported asbestos exposure (p=0.0419), presymptomatic anemia (p=0.0007), and epithelioid tumor histology (p=0.0001). Loss of 22q was unrelated to most clinical factors explored, being only marginally associated with N2-N3 lymph node status compared to N0-N1 (p=0.0429). Survival analysis showed that patients with CDKN2A loss, with (n=228) or without (n=101) concurrent loss of 22q, demonstrated reduced OS compared to patients with wild-type copy numbers (hazard ratio (HR) 1.6, 95% confidence interval (CI) 0.98-2.6, p=0.05). Conclusion: This study demonstrates a previously unappreciated relationship between demographic, clinical, pathological and outcome characteristics of MPM in association with CDKN2A versus 22q loss. The pattern of alteration involving these chromosomal regions may, therefore, suggest the possibility of distinct molecular subgroups. Further analyses are needed to demonstrate its potential role in precision medicine.

**Keywords:** CDKN2A, 22q, Mesothelioma, FISH

**PUB052 PROTEOME SIGNATURES AND NEW CANCER DRIVERS**

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**Background:** The ability to establish a primary tumor-derived xenograft is a poor prognosis indicator in early stage non-small cell lung carcinoma (NSCLC) and other cancers, suggesting engraftment selects for aggressive aspects of the cancer phenotype linked to disease progression. We hypothesized that engrafting NSCLC have distinctive proteomic features which may reveal novel cancer drivers. We contend proteome signature discovery is a vital component of an “integrated omics” platform, and broadly applicable to various types of cancer. **Methods:** 52 NSCLC primary tumors were analyzed by a quantitative proteomics approach called SILAC, which allowed for labeling a mixture of phosphorylated and non-phosphorylated protein from native tumors. **Results:** 52 NSCLC primary tumors were analyzed by a quantitative proteomics approach called SILAC, which allowed for labeling a mixture of phosphorylated and non-phosphorylated protein from native tumors. **Conclusion:** As of today, we do not identify KRAS- and TP53-mutated tumors. However, proteins associated with the mutation status may be new potential therapeutic targets to circumvent treatment resistance. In the present study, we identified both known and novel proteins associated with TP53 and KRAS mutated samples.

**Keywords:** NSCLC, proteomics, Prognosis, patient primary tumor-derived xenograft

**PUB053 PANEL BASED HYBRID CAPTURE SEQUENCING ASSAY TO CORRELATE MUTATIONAL LOAD WITH RESPONSE TO IMMUNOTHERAPY**

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**Background:** The use of immune checkpoint inhibitors has shown promise in lung cancer as well as several other tumor types. However, two of their limitations are the overall relative low response rate as well as the lack of powerful predictors for response. Recently, several studies have shown that stratification of patients according to the load of somatic mutations can provide predictive information for either ‘mono’ or ‘combinational’ immunotherapy. Here, we describe the use of a hybrid-capture based next-generation sequencing assay to stratify NSCLC patient cohort, and a determination of the consequences of signature protein modulation on in vitro and in vivo cancer phenotypes. **Results:** Proteomes of engrafting NSCLC tumors were different from non-engrafting tumors. Most significantly altered was a signature comprising certain metabolism proteins. High-level expression of one particular metabolism protein in non-engrafting tumors was validated in an independent NSCLC cohort for association with better survival by tissue microarray analysis. Ectopic expression of the protein inhibited NSCLC cell proliferation in vitro and xenograft tumor growth in vivo. **Conclusion:** We concluded that aggressive NSCLC have a unique proteome signature indicative of an altered metabolic state linked to patient prognosis. An enzyme, not previously implicated by genomic or transcriptomic analyses, is implicated as a negative cancer driver in NSCLC. Our results illustrate the power of proteomics to uncover cryptic cancer drivers, and portend innovative anti-metabolism therapeutic modalities.

**Keywords:** NSCLC, proteomics, Prognosis, patient primary tumor-derived xenograft
CANCER PUB055 THE 3Q26 ONCOCASSETTE: A MULTIGENIC DRIVER OF LUNG CANCER
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Background: Recurrent copy number variations (CNVs) are genetic alterations commonly observed in human tumors. One of the most frequent CNVs in human tumors involves copy number gains (CNGs) at chromosome 3q26, which is estimated to occur in >20% of all human tumors and >75% of lung squamous cell carcinoma (LSCC). The high prevalence and frequent occurrence of 3q26 CNG suggest that it drives the biology of tumors harboring this genetic alteration. The amplified chromosomal region (the 3q26 amplicon) spans from chromosome 3q26 to q29, a region containing ~200 protein-encoding genes. A number of genes in this region have been individually implicated in the transformed phenotype, and recent studies indicate an oncogenic cooperativity among a subset of the genes within the 3q26 amplicon.

Methods: A bioinformatics approach was utilized to identify potential driver genes within the recurrent 3q26 amplicon in LSCC. LSCC tumors with 3q26 CNGs were identified in The Cancer Genome Atlas (TCGA) dataset. Gene expression analysis was used to identify LSCC 3q26 genes with amplification-driven overexpression. Results: Our analysis reveals that a subset of amplified 3q26 genes are overexpressed in LSCC and reside on the LSCC susceptibility loci on mouse chromosome 3. Pathway analysis reveals that 21 of these genes exist within a single predicted cancer network module. Interestingly, four 3q26 genes, SOX2, ECT2, PRKCI and PI3KCA, occupy the hub of this network module and serve as nodal genes around which the network is organized. Integration of available genetic, genomic, biochemical and functional data demonstrate that SOX2, ECT2, PRKCI and PI3KCA are cooperating oncogenes that function within an integrated cell signaling network that drives a highly aggressive, stem-like phenotype in LSCC tumors harboring 3q26 amplification. Conclusion: The high level of integration amongst these 4 3q26 nodal genes suggests that they are the key oncogenic targets of the 3q26 amplicon and together define a “3q26 OncCassette” that mediates 3q26 CNG-driven LSCC tumorigenesis. Genomic analysis indicates that the 3q26 OncCassette also operates in other major tumor types that exhibit frequent 3q26 CNVs, including head and neck squamous cell carcinoma (HNSCC), ovarian serous cancer and cervical cancer. This study suggests that therapeutic targeting of the integrated oncogenic signaling of the 3q26 OncCassette will be a promising intervention strategy for improving treatment of 3q26-driven cancers.

Keywords: copy number gain (CNG), 3q26 amplicon, Lung Squamous cell carcinoma, Oncogenic driver
Background: Decision of salvage therapy for lung cancer recurrences is a major problem because of poor results with re-treatments having greater risk of side-effects. Stereotactic body radiotherapy (SBRT) is a promising technique in re-irradiation of lung cancer recurrences. In this study, we intend to present our results, including the toxicity and outcome of our patients treated with SBRT after radiotherapy failure. Methods: 403 patients were treated with SBRT for lung cancer at our department between June 2010 and August 2015. Among these, we identified 16 patients who were re-irradiated using SBRT. PET-CT was used in staging in all patients. All patients had recurrent disease only within the previous radiotherapy treatment volume. The median previous EBRT dose was 66 Gy (range, 46 - 66 Gy). Tumor responses were evaluated with PET-CT 3 months after SBRT and with computerized tomography (CT) every 3 months interval. Outcomes analyzed were grade 3 radiation pneumonitis, overall survival (OS), local control (LC), progression free survival (PFS) and distant metastasis. Results: The median follow-up time was 30 months from salvage SBRT. The locations of recurrent tumors were central in 12 and peripheral in 4 patients. The median largest tumor size was 4.35 cm (range: 1.4 and 6.6 cm) and planning target volume was median 67.3 cm³. The median SBRT dose was 38 Gy (range; 30 - 606Gy). Total biological equivalent dose (BED) was 63 Gy10 (range; 48 - 115 Gy10) and SBRT was applied after a median time of 12 months (range; 3-36 months) from prior radiation. Complete response was in 13, partial response was in 2, stable or progressive disease was observed in 1 patient. The 1 year, 2 year and 3 year LC rate was 93.8%, 85.2% and 85.2% respectively. The 1 year, 2 year and 3 year OS rate was 87.5% - 67.3% and 40.4% respectively. One and 3-year PFS rates were 49.2% and 28.1% respectively. At the last follow-up 5 patients were alive with no evidence of disease and one patient was alive with systemic metastases. The rate of symptomatic grade 3 pneumonitis was 12.5% and one patient developed fatal pneumonitis. Symptomatic grade 3 chest wall pain or esophagitis was not observed. Conclusion: Salvage therapy with re-irradiation with SBRT technique for in-field recurrent lung tumors appears to be a effective and well-tolerated option for cautiously selected patients even centrally located. Our results suggest that lower BED doses could still provide excellent LC for recurrent lung tumors in the previous RT field with an acceptable complication rate. Keywords: Recurrent lung cancer, stereotactic body radiotherapy, SBRT

Fig 1. Lung-window CT scan shows multiple cystic changes in the both sides of the lung.

Fig 2. Immunohistochemical staining for cytokeratin 7 (CK7) and CK20 were positive. The patient was a 67-year-old woman. A computed tomographic scan of the chest revealed multiple cystic changes in the both sides of her lung (Fig 1). Tumor markers such as CEA, cyfra211 and SCC were mild elevated. Sputum cytology and transbronchial examination didn’t find cancer. PET-CT revealed high FDG accumulation at the lesion in the lung. She did the CT guided lung biopsy. Histopathologically, the tumor consisted predominantly of colorectal carcinoma-like components, composed mainly of tall columnar cells with a brush-border and eosinophilic cytoplasm. Immunohistochemical staining for CK7 and CK20 were positive (Fig 2), whereas TTF-1 and napsin-A were negative. The final diagnosis was primary pulmonary intestinal-type adenocarcinoma. Conclusion: There are few reported cases of pulmonary intestinal-type adenocarcinoma. More experience of such cases is needed to further understand this rare variant of adenocarcinoma.
Background: Recent studies have reported that the sonic hedgehog (Shh) signaling pathway plays a crucial role during tumorigenesis, angiogenesis and cellular differentiation in various malignancies including lung cancer. The aim of this study is to investigate the value of Shh pathway as prognostic markers in extensive stage small lung cancer (ES-SCLC) patients. Methods: We retrospectively analyzed the data of 36 patients with ES-SCLC between 2008 and 2012 in Komagome Hospital. Formalin fixed paraffin embedded tissues of primary tumors, immunohistochemistry was done for Gli1, Patched, Shh, and Smo. We performed survival analysis to obtain the prognostic impact of these markers. Results: All the 36 patients were treated with platinum based doublet chemotherapy. Median progression free survival and median overall survival was 6.9 months (95% CI, 6.5-7.3) and 11.7 months (95% CI, 9.1-14.3), respectively. Overall response rate was 84%. Of the 36 specimens examined, the overexpression of Gli1, Patched, Shh, and Smo was found in 12 (33.3%), 5 (13.9%), 5 (13.9%), and 6 (16.7%), respectively. We found that high expression of Smo was associated with worse progression free survival (6.9 vs. 7.6 months, p<0.01) and overall survival (9.2 vs. 12.0 months), whereas other markers were not related to the prognosis of patients. Conclusion: To our knowledge, this is the first report of the relationship between components of the Shh signaling pathway and prognosis in SCLC. We found that a high proportion of tumors expressed proteins related to this pathway, and over-expression of Shh was correlated with worse survival in this analysis. Shh signaling in SCLC requires further investigation using a larger sample size.

Keywords: Small Cell Lung Cancer, Prognosis, Biomarker

Background: Brain metastasis (BM) remains a therapeutically challenging issue, which often predicts poor prognosis. Moreover, there are still some patients developing BM during the course of EGFR-TKIs therapy, although EGFR-TKIs are effective for EGFR-mutated NSCLC patients with BM. Therefore, controversial value of prophylactic cranial irradiation (PCI) in NSCLC in terms of survival benefit prompted us to explore the possible risk factors for BM during the course of EGFR-TKIs therapy from EGFR-mutated advanced lung adenocarcinoma and identify the potential population most likely to benefit from PCI. Methods: We retrospectively reviewed the records of 134 patients with EGFR-TKIs therapy from EGFR-mutated advanced lung adenocarcinoma between 2008 and 2012. Among them, 78 patients (58.2%) were confirmed to have EGFR exon 19 point mutations, while 56 patients (41.8%) had EGFR exon 21 point mutations. The cumulative incidence of BM was calculated by the Kaplan–Meier method and differences between the groups were analyzed using the log-rank test. Multivariate Cox regression analysis was used to assess the independent risk factors of BM. Results: Thirty-four patients (34/134, 25.4%) developed BM during the course of EGFR-TKIs therapy. Multivariate analysis indicated that age ≥53 years (HR: 2.76, 95% CI: 1.326-5.707; p = 0.007), serum carcinoembryonic antigen (CEA) ≥23 ng/mL (HR: 1.92, 95% CI: 1.125-3.248; p = 0.011) and EGFR exon 21 point mutations (HR: 2.76, 95% CI: 1.355-5.659; p = 0.005) were the independent high-risk factors for developing BM, which could offer important insights into the individualized treatment. Conclusion: Patients, with age ≥53 years, CEA ≥23 ng/mL and exon 21 point mutations from EGFR-mutated advanced lung adenocarcinoma, are at the highest risk for developing BM during the course of EGFR-TKIs therapy, and are most likely to benefit from PCI. Additionally, further studies are warranted to validate our findings.

Keywords: brain metastases, risk factors, Epidermal growth factor receptor, advanced lung adenocarcinoma

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PUB062 RISK FACTORS OF BRAIN METASTASIS DURING THE COURSE OF EGFR-TKIS THERAPY FOR PATIENTS WITH EGFR-MUTATED ADVANCED LUNG ADENOCARCINOMA

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Background: Brain metastasis (BM) remains a therapeutically challenging issue, which often predicts poor prognosis. Moreover, there are still some patients developing BM during the course of EGFR-TKIs therapy, although EGFR-TKIs are effective for EGFR-mutated NSCLC patients with BM. Therefore, controversial value of prophylactic cranial irradiation (PCI) in NSCLC in terms of survival benefit prompted us to explore the possible risk factors for BM during the course of EGFR-TKIs therapy from EGFR-mutated advanced lung adenocarcinoma and identify the potential population most likely to benefit from PCI. Methods: We retrospectively reviewed the records of 134 patients with EGFR-TKIs therapy from EGFR-mutated advanced lung adenocarcinoma between 2008 and 2012. Among them, 78 patients (58.2%) were confirmed to have EGFR exon 19 point mutations, while 56 patients (41.8%) had EGFR exon 21 point mutations. The cumulative incidence of BM was calculated by the Kaplan–Meier method and differences between the groups were analyzed using the log-rank test. Multivariate Cox regression analysis was used to assess the independent risk factors of BM. Results: Thirty-four patients (34/134, 25.4%) developed BM during the course of EGFR-TKIs therapy. Multivariate analysis indicated that age ≥53 years (HR: 2.76, 95% CI: 1.326-5.707; p = 0.007), serum carcinoembryonic antigen (CEA) ≥23 ng/mL (HR: 1.92, 95% CI: 1.125-3.248; p = 0.011) and EGFR exon 21 point mutations (HR: 2.76, 95% CI: 1.355-5.659; p = 0.005) were the independent high-risk factors for developing BM, which could offer important insights into the individualized treatment. Conclusion: Patients, with age ≥53 years, CEA ≥23 ng/mL and exon 21 point mutations from EGFR-mutated advanced lung adenocarcinoma, are at the highest risk for developing BM during the course of EGFR-TKIs therapy, and are most likely to benefit from PCI. Additionally, further studies are warranted to validate our findings.

Keywords: brain metastases, risk factors, Epidermal growth factor receptor, advanced lung adenocarcinoma

PUB063 PD-L1 EXPRESSION LEVEL COULD PREDICT THE SURVIVAL OF PATIENTS WITH RESECTABLE SMALL CELL LUNG CANCER

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Background: Several studies indicated PD-L1 expression on tumor cells is the potential predictive biomarker. However, the prevalence of PD-L1 expression in small cell lung cancer (SCLC) is unclear. This retrospective study aims to detect PD-L1 expression in patients with resectable SCLC and investigate the correlation between PD-L1 expression and the survival of patients. Methods: Formalin-fixed, paraffin-embedded samples were stained with PD-L1 antibody by immunohistochemical (IHC) analysis (M4424 antibody). IHC score was calculated according to staining intensity and the percentages of staining tumor cells. Kaplan–Meier method and Cox proportional hazards model analyses were used to evaluate the role of PD-L1 expression on the prognosis of patients with SCLC. Results: From 2011-2013, totally 61 patients (43 males/18 females) who underwent complete resection were collected with median age 56 years (range, 30-74) at the time of diagnosis. For the whole group, 32.8% (20/61), 27.5% (17/61) and 39.3% (24/61) patients were diagnosed as pathological stage I, II and III. Until the end of follow-up, 60.7% (37/61) patients are alive. For entire group, the median survival time (MST) was not reached (NR), range (6.13-2.5 months); 3- and 5-year survival rates were 57.3% and 54.2%, respectively. For the whole cohort, 57.4% (35/61), 37.7% (23/61) and 21.3% (13/61) patients expressed PD-L1 ≥1%, 5% and 10%, respectively, and 3-year survival rate was 60.0%, 72.3% and 47.0%, respectively. When the positivity threshold of PD-L1 expression was defined as PD-L1 expression ≥5%, the MST in patients with PD-L1 (+) tumors was significantly longer than that with PD-L1 (-) tumors (NR vs. 34 months, p = 0.032). No significantly survival differences were observed when PD-L1 positivity threshold was defined as 1% or 10%. For patients with stage I SCLC, the MST in patients with PD-L1 expression ≥5% was significantly longer than that in patients with PD-L1 expression ≤5% (NR vs. 56 months, p = 0.03). Regardless of the positivity threshold of PD-L1 expression with 1%, 5% or 10%, for patients with stage II or III SCLC, no significant survival differences were observed. Multivariate analysis indicated postoperative chemotherapy (hazard ratio [HR] = 0.322, p = 0.023), PCI (HR = 0.105, p = 0.029) and PD-L1 expression (HR = 0.253, p = 0.008) were independent prognostic factors for OS. Conclusion: PD-L1 highly expressed in patients with resectable SCLC. The level of PD-L1 expression could predict the survival of patients in this setting.

Keywords: SCLC, PD-L1, Prognosis factor;
**Abstracts**

**PUB064 CORRELATION BETWEEN ESTROGEN RECEPTOR ALPHA AND BETA AND THE MARKERS COEXPRESSION IN NON- small Cell Lung Cancer (NSCLC) Tissue**

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**Background:** The results of chemotheraphy of NSCLC are not satisfactory enough that is why new approaches are needed and perspective hormonal therapy strategy implying estrogen receptors (ER) as drug target is investigated. Previously we have revealed the high level of tumor ER beta expression in about half of patients with NSCLC. But taking into account that ER alpha are also targets for estrogens and antiestrogens action we have studied tumor expression of both types of ER in the same patients in order to estimate correlation between ER alpha and ER beta expressions and targets coexpression frequency. **Methods:** NSCLC surgical biopsy specimens (n=90) were analyzed by flow cytometry. Single-cell suspensions were incubated with primary antibodies (14C8, Abcam) overnight and with secondary DyLight 650-conjugated antibody (ab98729, Abcam) for 1.5h. Cell fluorescence was analyzed by Flowjo 10.1 software and Kolmogorov-Smirnov statistical approach. Three levels of ER expression were distinguished: high – ER were revealed more than in 45% of the cells; moderate – in 30-44%; low - in 11-29%. ER expression level less than 10% was considered as negative. Spearman rank correlation coefficient (rs) was used for estimation of dependence between expressions of ER alpha and ER beta. **Results:** 1. ER beta was revealed in all the specimens, but ER alpha – in 89% only. 2. Median of ER alpha level was about two times lower as compared to ER beta (19% vs. 44%). 3. Low ER alpha expression was revealed 2.9 times often compared to ER beta (70% vs. 24%). Opposite, high expression of ER alpha was 4.3 times rarely compared to ER beta (11% vs. 47%) and moderate index – 1.5 times rarely (19% vs. 29%). 4. Coexpression of high or moderate ER alpha expression was found in 33% of the tumors with high ER beta expression. 5. Moderate correlation between ER alpha and ER beta expression was found (rs=0,51; 95% CI 0,4-0,76, p=0,03). **Conclusion:** NSCLC is actually ER-positive tumor with higher frequency and level of ER beta expression compared to ER alpha. Established correlation between ER beta and ER alpha expression indicates a common mechanism of their regulation in the NSCLC tissue. We postulate that at least about half of the NSCLC patients with high ER beta expression and especially 1/3 of them with high and moderate index ER coexpression could benefit from adjuvant antiestrogen treatment. Supported by RFBR grants (15-04-06991-a, 16-34-01049 mol-a) and President of Russian Federation grant MK-7709.2016.7.

**Keywords:** non-small cell lung cancer, ER alpha, ER beta, flow cytometry

**PUB065 MIR-26A DESENSITIZES NON-SMALL CELL LUNG CANCER CELLS TO TYROSINE KINASE INHIBITORS BY TARGETING PTPN13**

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**Background:** Epidermal growth factor receptor (EGFR)-driven lung cancers are among the most threatening malignancies with extremely high mortality. Despite the successful application of tyrosine kinase inhibitors (TKIs) in treating these carcinomas, the therapeutic efficacy of EGFR-TKIs has been compromised by frequently occurring drug resistance. The mechanisms that maintain cell survival and cause sustained proliferation upon TKI treatment remain to be fully understood. **Methods:** Cell culture, western blot, bioinformatic study, luciferase reporter assay and xenograft model study were employed in this study. **Results:** In this study, we found that mir-26a was upregulated in some TKI-refractory NSCLC cells; mir-26a directly targets and silences protein tyrosine phosphatase non-receptor type 13 (PTPN13) to maintain the activation of Src, a dephosphorylation substrate of PTPN13. Whereas mir-26a is upregulated by EGFR signaling, EGFR/mir-26a/PTPN13/Src forms a feedforward circuit to reinforce EGFR pathway, which circumvents the complete suppression of EGFR signaling and cell proliferation by TKIs. **Conclusion:** In conclusion, our findings unraveled a novel mechanism underlying the resistance of lung cancers to TKIs, and thus have implications for mir-26a as a predictive biomarker and a synergistic target for EGFR-inhibiting therapy of lung cancers.

**Keywords:** Epidermal growth factor receptor, non-small cell lung cancer, miR-26a, protein tyrosine phosphatase non-receptor type 13

**PUB066 YOGA AS A POWERFUL TOOL FOR SMOKING CESSATION - CONVINCING RESULTS OF A COMMUNITY BASED RANDOMISED CONTROLLED TRIAL**

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**Background:** Almost 47% smokers in India want to quit (GATS, 2010), if they are able to. Smokers have faced difficulty in quitting due to issues like anxiety, restlessness, insomnia, irritability, depression, anger, lack of concentration and difficulty in resisting craving. Yoga, an ancient science of well-being...
that developed in India, has long been known to bring peace, vitality and tranquility on regular practice. Hence, it is expected that practising yoga should help a smoker in quitting. To scientifically evaluate the proposition of yoga as an aid for smoking cessation, a randomized controlled trial has been performed by the authors. **Methods:** A total of 124 `current smokers` who expressed self-intent to quit were recruited into study from the community through resident-welfare organizations in Gurgaon, India. Participants were randomized to one of the 2 intervention arms, 62 each. All participants were offered bi-weekly counselling at 0, 2, 4, 8 and 12 weeks. In addition to behavioural counselling, 62 participants were linked to a Yoga Ashram (Institute) for twice a week one-hour yoga classes. Yoga group participants were offered dhyaa(meditation), pranayama(breathing exercises) and asanas(physical pose-based exercises) as a holistic wellness approach. Outcome measure included 7 day point-prevalence abstinence (as reported by participants) at end of 4 weeks, 8 weeks and 12 weeks. **Results:** A total of 106 participants completed the study. Attendance in yoga classes varied from 64% to 100% in the Yoga group. At the end of 4 weeks, participants in the yoga group exhibited increased odds of 7 day point-prevalence abstinence as compared to those in ‘only behavioural counselling’ group (Odds Ratio: 4.2, 95% CI: 1.6 - 7.4). Participants in the yoga group continued to exhibit higher odds of being abstinent at the end of 8 weeks (Odds Ratio: 3.1, 95% CI: 1.2 - 6.4) and 12 weeks (Odds Ratio: 2.9, 95% CI: 1.2 - 6.7). **Conclusion:** Results of this study indicate that incorporating yoga as a component of smoking cessation programs has potential to significantly improve the outcome. With the world formally accepting Yoga and UN declaring 22 June as International Yoga Day, time is now even more appropriate for all countries to exploit the benefits offered by Yoga towards smoking cessation. Self-report can be a feasible method to assess the benefits of incorporating Yoga as a component of smoking cessation programs has potential to significantly improve the outcome. With the world formally accepting Yoga and UN declaring 22 June as International Yoga Day, time is now even more appropriate for all countries to exploit the benefits offered by Yoga towards smoking cessation.

**Background:** Lung cancer is one of the commonest cancer worldwide contributing to 13% of the total number of cancers (1). It is the leading cause of cancer related death in the United Kingdom with poor 10 year survival rate of 5% (2). Advanced age and the presence of comorbid conditions are associated with poor survival rate. The use of Platinum based chemotherapy in advanced non-small cell lung cancer (NSCLC) has improved survival rate and improve the quality of life. However, these effects are limited by the chemotherapy induced toxicity. Prior to commencement of chemotherapy, there is no current method which can be used to predict the development of unacceptable level of chemo-toxicity that might subsequently result in reducing or stopping the chemotheraphy treatment. This study aims to correlate platinum-based chemotherapy haematological and non-haematological toxicities in patients with NSCLC against two commonly used comorbidity indices namely Charlson Comorbidity Index (CCI) and the Adult comorbidity Evaluation 27 (ACE 27). **Methods:** Case note review for patients with cytologically or histologically confirmed NSCLC, aged between 18 and 85 with a World Health Organisation performance status (WHO PS) of ≤ 2, eligible for platinum based chemotherapy and have a life expectancy > 3 months. Exclusion criteria include the presence of an active infection and those who received platinum-based chemotherapy previously. Patients were identified from the combined lung cancer clinics and multidisciplinary meetings and were invited to participate in the study. Baseline demographic data (age, sex, PS, cancer stage and type) was obtained. CCI and ACE 27 tools were used to score baseline comorbid conditions for each patient with and without the inclusion of the disease. After each chemotheraphy cycle, haematological and non-haematological toxicity data was collected. The time of diagnosis, treatment and survival was monitored in a prospective manner. All grades of thrombocytopenia, together, had prognostic factor, but patients with higher grades of thrombocytopenia had statistically significant better survival.

**Background:** Chemotherapy induced thrombocytopenia (CIT) is a common side effect of chemotherapy (HT), and it is believed that thrombocytopenia during HT is a independent prognostic factor in lung cancer patients. The aim of this study was to determine the influence of thrombocytopenia during HT as a prognostic factor in patients with non-small cell lung cancer (NSCLC). **Methods:** The study was non-randomized, retrospective–prospective and conducted in the Institute for Pulmonary diseases in Sremska Kamenica. The study included 100 NSCLC patients, clinical stages III and IV, who were treated with protocol gemcitabine/cisplatin in first line setting. Study group consisted of 50 patients with, and control group of 50 patients without hematological toxicity during HT. Survival was monitored in a prospective two-year period. **Results:** There were 76% males and 24% females in the sample. The most frequent were patients in stage IV (52%), and the most common histological type was adenocarcinoma (67%). The initial value of platelets did not affect the occurrence of thrombocytopenia all grades during HT (p<0.72), while the starting thrombocytosis was a negative prognostic factor (p=0.012). All grades of thrombocytopenia, together, had prognostic significance (p<0.025), while multivariate analysis has not been established that thrombocytopenia is independent prognostic factor (p=0.683).

**Conclusion:** Thrombocytopenia is not an independent prognostic factor, but patients with higher grades of thrombocytopenia had better survival.
PUB070 AICINAR-PREDOMINANT PATTERN CORRELATES WITH POORER OUTCOME IN INVASIVE MUCINOUS ADENOCARCINOMA OF THE LUNG

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Background: Invasive mucinous adenocarcinoma (IMA) is a variant of lung adenocarcinoma. Growth pattern such as lepidic, acinar, papillary and micropapillary can be seen in IMA. However, no study regarding prognostic and clinicopathologic aspects of IMAs with different growth pattern has been reported. Methods: From January 1999 to July 2011, of 2236 patients with newly diagnosed primary lung adenocarcinoma, 16 patients were identified as lepidic-predominant IMA and 10 patients as acinar-predominant IMA. Data regarding the clinicopathological characteristics, CT features and prognosis was collected. Results: No statistically significant difference was noted in gender, age as well as smoker proportion between lepidic-predominant and acinar-predominant IMA. There was no statistically significant difference in T classification. The proportion of lymph node metastasis was significantly higher in acinar-predominant IMA (P=0.046). Both the tumors shared many signs in CT findings. Air-bronchogram was a relatively specific sign for lepidic-predominant IMA. Survival analysis showed that lepidic-predominant IMA also have a more favorable outcome than acinar-predominant IMA (P=0.0294).

Conclusion: Lepidic-predominant and acinar-predominant IMA are two different subtypes of IMA. Acinar-predominant IMA is associated with lymph node metastasis and has a poorer prognosis than lepidic-predominant IMA.

Keywords: invasive mucinous adenocarcinoma, lung adenocarcinoma, pathological subtype, Prognosis

PUB071 FRAGILE-SITE ASSOCIATED TUMOR SUPPRESSOR (FATS) GENE EXPRESSION EFFECT ON THE SENSITIVITY OF CISPLATIN AND GEMCITABINE IN ADVANCED NSCLC

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Background: Cisplatin and Gemcitabine chemotherapy regimen has been the standard of care for the treatment of advanced stage non-small cell lung cancer but not all patients respond adequately to the treatment. We therefore assessed the expression of FATS (Fragile-site associated tumor suppressor) gene and the response to cisplatin and gemcitabine. Methods: A prospective longitudinal study has been conducted in NCI (National Cancer Institute) medical oncology department in outpatient setting in the period between June 2012 and July 2014. The study included 70 patients with pathologically proven advanced (stage IIIb and IV) NSCLC treated with cisplatin and gemcitabine. FATS gene expression was measured before starting the treatment. The primary end point was overall response rate (ORR) while the secondary end point was progression free survival (PFS) and overall survival (OS). Results: 70 patients were assessed and included in the trial. 13 patients achieved partial response while 13 patients achieved stable disease and the rest had progressive disease. The overall response rate was significant (p-value 0.031) for the high FATS expression group. The median PFS was 4.1 months (95% CI 2.1-6.2) in the low expression group and 3.8 months (95% CI 3.3-4.3) in the high expression group (p-value 0.442) while median OS was 6.9 months (95% CI 5.4-8.3) in the high expression group and 4.5 months (95% CI 3.7-5.3) in the low expression group (p-value 0.031)

Conclusion: The expression of the FATS gene can have an implication on the response to cisplatin-gemcitabine and the overall survival. This opens the opportunity that FATS gene can be used as a predictive marker for NSCLC patients receiving cisplatin and gemcitabine chemotherapy

Keywords: Cisplatin, Gemcitabine, NSCLC, FATS

PUB072 DYNAMIC MONITORING OF EGFRMUTATION IN PLASMA CELL-FREE DNA BY DIGITAL PCR

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Background: Non-small cell lung cancer (NSCLC) represents approximately 85% of all lung cancers, which are the leading cause of cancer-related deaths in the world. Fortunately, EGFR-TKIs are dramatically effective in lung cancer with EGFR activating mutations. However, even in cases where there is high effectiveness, tolerance is acquired within 6 months to 12 months. Therefore, it’s necessary to test EGFR mutation for identifying the right patients before EGFR-TKI treatment and monitor the EGFR mutation status during treatment. Nowadays, EGFR mutation testing in plasma cell-free DNA (cfDNA) from lung cancer patients is emerging as a valuable clinical tool. A new generation of PCR technique ddPCR were developed, which enabled the highly sensitive genotyping and the absolute quantification of mutant genes. Methods: This study investigated the quantification and dynamic change of EGFR mutation status in plasma cfDNA by ddPCR technology to assess the clinical response of EGFR-TKI therapy in NSCLC patients. 1. We retrospectively investigated 50 patients with NSCLC for their EGFR sensitive mutations and T790M mutation in matched pre-, during- and post-TKI plasma samples, using ddPCR technology; 2. We retrospectively investigated 158 patients with NSCLC who ever received Erlotinib treatment and analyzed the survival curves of different EGFR mutation status (E19-Dels, L858R, negative). Results: 1. For E19-Dels and L858R, the plasma testing sensitivity and specificity, compared to the matched tumor tissues tested by ARMS, were 41.30% and 88.89%. The status of EGFR mutation changed according to the clinical response to Erlotinib for 8 of 9 patients. The study also demonstrated that monitoring the EGFR mutations in the blood allows for the detection of the T790M mutation up to 18 weeks before disease progression is clinically evident. At the time of disease progression the T790M mutation was detected in plasma from 6 patients (50%). There was no significant differences of PFS between E19-Dels and L858R (42±9.7 vs 97.0±113). For NSCLC patients without EGFR activating mutation, DCR was 52.4% (95% CI 33.2–76.9). The median PFS and OS were 20 weeks and 51 weeks. Conclusion: Qualitative and quantitative detecting of EGFR gene mutation by the highly sensitive and specific ddPCR assays provided a non-invasive assay to predict EGFR-TKI prognosis.
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PUB073 STATINS DOSE-DEPENDENTLY EXERTS A SIGNIFICANT CHEMOPREVENTIVE EFFECT AGAINST LUNG CANCER IN COPD PATIENTS: A POPULATION-BASED COHORT STUDY
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Background: Chronic obstructive pulmonary disease (COPD) is independently associated with an increased risk of developing lung cancer. In this study, we want to evaluate the association of statins as a chemoprevention of lung cancer in COPD patients and investigate which one of statin has larger chemopreventive effect. Methods: The study cohort comprised all patients diagnosed with COPD according to International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes at healthcare facilities in Taiwan (n = 116,017) from January 1, 2001, to December 31, 2012. Our final study cohort contained 43,802 patients diagnosed with COPD in Taiwan over the 11-year period; 10,086 COPD patients with statins use and 33,716 COPD patients without statins use. Each patient was followed up to assess the risk of lung cancer or protective factors: the demographic characteristics of age and sex; the comorbidities of diabetes, hypertension, dyslipidemia, Charlson Comorbidity Index; urbanization level; monthly income; and non-statins lipid-lowering drugs, metformin, aspirin, and angiotensin-converting enzyme inhibitor (ACEI) use. The index date of statins use was the date of COPD confirmation. To examine the dose-response relationship, we categorized statins use into four groups in each cohort (<28, 28–90, 91–365, and >365 cumulative [C]DDD). Results: Patients who received >28 CDDD were defined as non-statins users. Results: After adjustment for sex, Charlson comorbidity index, diabetes, hypertension, dyslipidemia, level of urbanization, Monthly income in propensity score, we analyzed the risk of lung cancer. The adjusted HRs (aHRs) of lung cancer decreased in statins use patients compared with those in non-statins use patients (aHRs = 0.37, 0.95 CI: 0.31, 0.64). In different individual statins use, lovastatin and fluvasatin could not reduce the risk of lung cancer in COPD patients, statistically. The adjusted aHRs of lung cancer decreased in individual statins use patients compared with those in non-statins use patients (rosuvastatin, simvastatin, atorvastatin and pravastatin: aHRs = 0.41, 0.44, 0.52 and 0.58, respectively). After sensitivity analysis, statins dose-dependently reduced the risk of lung cancer in all subgroups and the main model with additional covariates (non-statins lipid-lowering drugs, metformin, ACEI, or aspirin use). Conclusion: Statins dose-dependently exerts a significant chemopreventive effect against lung cancer in COPD patients. The priority of chemopreventive potent were rosuvastatin, simvastatin, and atorvastatin in this study.

Keywords: statins, copd, lung cancer, Dose

PUB074 INTAKE OF COLD HIGH DISSOLVED OXYGEN MINERAL WATER AS CANCER CURE
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Background: Section not applicable Methods: Many known cancer treatment methods rely on oxygen and/or ozone cancer treatment by gas and by liquid have demonstrated varying degree of successes. A new innovative approach is being applied relying on nano bubble water with high oxygenated level up to 15 to 20 ppm. Normal dissolved oxygen in water seldom exceed 10 ppm. Dissolved oxygen exceeding 10 ppm is in the form activated oxygen (inside nano bubbles) which has ORP value of +2.5V. Nano bubbles can penetrate all types of human membrane and provide oxygen into cancer cells which will cause cell death while healthy cells will prosper. These nano bubble will contain beneficial levels of dissolved nano nitric oxide which will enlarge blood vessels surrounding the cancer cell clusters which speed up the cure. In combination with fasting (no food intake except water) for 14 days, the human body will conduct self detoxification processes and expell toxins out through urine and excretion. Excretion will stop after 2 to 3 days of fasting. These samples analysis yielded various environmental, growth hormones, pesticides and antibiotics residues. Results: Treatment of terminal lung cancer patients with lung cancers showed either shrinkage or even disappearance. Several representative lung cancer cure cases will be presented with varied degree of successes. Conclusion: Drastic cancer cures means shorter hospital stay. However, bad living habits like eating fatty food, alhohols, smoking patients may need regular maintenance of drinking high oxygenated water.

Keywords: high activated oxygen treatment, oxygenated water therapy, high dissolved activated-oxygen treatment
Conclusion: Surgical treatment is associated with a better survival of SCLC patients. The nomogram is an ideal prognostic prediction tool of OS for postoperative SCLC patients, which has better predictive accuracy than other classifications.

Keywords: SEER, SCLC, Surgery, Nomogram, Survival
Background: In a previous open-label, noninferiority trial, cytisine was found to be superior to nicotine-replacement therapy (NRT) in helping smokers quit smoking. There is no other study comparing the abstinence effectiveness of these medications in Russia. Cytisine and NRT are widely available as over-the-counter medications. A real-life study could provide clinicians/researchers with useful information as to the effectiveness of these medications among the general population. The present study aimed to compare past year 30-day and 90-day self-reported smoking abstinence rates for self-reported cytisine and NRT use in individuals who wanted to quit smoking, using a representative sample of the Russian Federation population. Methods: We selected individuals who have tried to quit smoking and who have used cytisine (n = 88) or NRT (n = 186) in the past year from a Russian nationally representative survey of adults 15 years of age or older by the GATS 2009 Russian Global Adult Tobacco Survey (GATS). All analyses were performed in STATA software taking into account complex survey design features. Multivariable logistic regression models were used to compare past year-use of cytisine and NRT for 30-day and 90-day self-reported smoking abstinence rates. Results: The NRT 30-day and 90-day self-reported smoking abstinence rates were 36.2% and 10.9%, respectively. The cytisine 30-day and 90-day self-reported smoking abstinence rates were 50.4% and 25.3%, respectively. After adjusting the logistic regression for other possible confounders, such as sociodemographic, smoking behavior and treatment variables, cytisine was more effective than NRT only for the 90-day smoking abstinence rate. Conclusion: Just one trial has compared cytisine with NRT. In this context, it is important to verify the superiority of cytisine on NRT for achieving 90-day smoking abstinence, using real-life data from a representative sample of the general population of a country where cytisine and NRT are widely available as over-the-counter medications. These results and those from previous studies call for cytisine licensing worldwide, especially outside Eastern Europe.

Keywords: Smoking Cessation, cytisine, epidemiology, nicotine replacement treatment

Background: As in any developing countries state of West Bengal in India has a huge burden of metastatic Lung cancer patients in advanced stage coming from rural area where awareness regarding the usefulness of palliative care in such patients is very poor. Our goal is to give a pain free good quality of life in these patients. Objective of this study is to identify the main difficulties in achieving the above goal in a rural setting in India. Methods: Advanced Lung cancer patients in need of palliative care in various villages in rural India were selected for this study. Their symptoms and management in that rural setting of about 15 years was evaluated by an NGO under the guidance of a senior palliative care specialist working in that area. An attempt was made to identify the main obstacles in getting proper palliative care in a rural setting. Results: Pain, fatigue, distress, effusion are the main symptoms affecting these patients. In most patients pain and other symptoms control was grossly inadequate due to lack of properly trained manpower in the rural India. However regular homecare visits by a group of social workers were of immense help in the last few months of life. NGO team was well guided by a palliative care specialist. Conclusion: There is a wide gap of trained manpower in this field in rural areas of India. Dedicated groups from rural area need encouragement, repeated home visit, awareness building up, training to home care giver, so that difficult symptoms can be managed locally along with necessary social and psychological support to these patients

Keywords: palliative care, NGO, supportive care, rural India

Background: EGFR-TKIs have been the standard first-line treatment for metastatic NSCLC patients with sensitive EGFR-mutants, meanwhile, other drugs target different driver mutants like BRAF-inhibitor dabrafenib has shown promising efficacy for metastatic BRAF-mutated NSCLC patients. Therefore, spotting patients carrying the targeted mutation is of great significance. However, molecular detection methods applied in clinical practice, especially detection of BRAF in NSCLC patients needs further exploration. Therefore, more sensitive and economic methods are required. Methods: We applied the CastPCR technology to the molecular detection of EGFR (del2235-2249, del2236-2250, T790M, L858R) and BRAF (V600E, G469A, DS94G) mutations in 144 treatment-naive adenocarcinomas of the lung, and analyzed the association between the mutation rates and patients’ clinicopathological features. Results: EGFR mutation: 74 (51.4%, 74/144) cases were identified harboring EGFR mutations. 58 (40.3%, 58/144) carrying sensitizing mutations (19Del or L858R) and 21 (14.6%, 21/144) carried resistant mutations (7790M). 10 (6.9%, 10/144) mutation-positive patients were double-mutated. EGFR mutation rate was significantly higher in female compared with that of males (60.9% v.s. 43.8%, P < 0.05), in non-smokers compared with that of smokers (62.8% v.s. 34.5%, P < 0.05). BRAF mutation:12 (8.3%, 12/144) patients were identified with BRAF mutation, 2 were V600E (16.7%, 2/12) and 10 (83.3%, 10/12) were non-V600E. Among the 10 non-V600E mutations, DS94G accounted for 9 (90.0%, 9/10) and G469A accounted for only 1 (10.0%, 1/10). Statistical analysis demonstrated that BRAF mutation rates was not associated with any of the clinicopathological features: age, gender, smoking status, differentiation degree, tumor size, regional lymph nodes metastasis and distant metastasis of (P > 0.05). Conclusion: The CastPCR technology is a robust method with high sensitivity for molecular detecting of EGFR and BRAF mutations in clinical FFPE samples. Keywords: EGFR, CastPCR, BRAF, lung adenocarcinoma

Background: In the FCT & MPOWER policy of WHO -W stands to Warn about hazards of Tobacco, specially the health hazards. Tobacco control is complex problem requires attention of all FCTC parties and NGO. Methods: Electronic media-specially TV media has the highest visibility, but, non aired mass media methods for creating awareness, has its own importance and many a times it is much cheaper and gets free coverage & easily available in different languages. Electronic media-specially TV media has the highest visibility; but, non aired mass media methods for creating awareness, has its own importance and many a times it is much cheaper and gets free coverage & easily available in different languages. Cancer Society of M.P. has been working in the field of Tobacco control for many years, using a combination of these different methodologies. Some of the activities conducted by us for Tobacco control and creating awareness about its health hazards are:- Posters: We have prepared, published and distributed various posters for tobacco control and self examination of oral cavity. Our posters have won international awards and have also been presented in many national & international conferences. The release of poster by eminent personalities, politicians gives us free media coverage on the topic too. One of our posters was also tested by Americans for its impact in Egypt. Hoardings/ Bill boards are a cheaper long term display media, strategically placed, it has a high visibility also. Pamphlets:- We have distributed nearly 100 thousand pamphlets in the holy Sinhastha Mela (fair) where nearly 10 million people participated. Hoardings/Bill Boards- Installed at strategic points they are a source of constant reminder to the health hazards of tobacco. Lectures/symposiums:- We regularly give lectures on different aspects of tobacco control & its health hazards. Exhibitions:- Participation & display of banners, posters etc in various exhibitions, where many people come & see them. Public Rally:- Rally taken out through the city draws attention of general public as well as gets free media coverage. Involvement of Priests- lectures given in various temples & holy places to involve priests into tobacco control. Lectures/symposiums/workshops- we have done more than 100 such activities, mainly targeting schools, colleges, social clubs, police, media, lawyers etc.

Keywords: Tobacco, Media
Abstracts

PUB081 DISCOVERY OF 1,3,5-TRIAZINE BASED NOVEL EGFR-TYROSINE KINASE INHIBITOR AGAINST HUMAN LUNG CARCINOMA
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Background: In India, the number of new lung cancer cases has been increased with an annual rise of 15-20%. This pose a significant burden on already struggling healthcare services of the country. Thus, more efforts have been directed towards the easy access of the medicines and development of novel cost effective drug for the under-privileged. Consequently, introduction of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) has led to dramatic clinical improvement in non-small cell lung cancer (NSCLC).

However, resistance to these inhibitors either via intrinsic and acquired resistance, put a selective pressure on the development of novel inhibitors. Therefore, the present study was aimed to develop novel 1,3,5-triazine derivatives as EGFR-TKIs for lung carcinoma. Methods: The 1,3,5-triazine compounds were synthesized via multi-component reaction. The compounds were tested for determination of anticancer activity three human NSCLC cell lines A549, H157 and H52. The compounds were also tested for effect on cell growth inhibition and apoptosis through cell cycle arrest assay. The docking analysis was also carried out with EGFR-TK domain (PDB ID: 1M17) to elucidate vital structural residues necessary for bioactivity. Results: The compounds were developed in excellent yield. The cytotoxicity studies suggest that, synthesized derivatives exhibit considerable inhibition with average IC50 for compound 7h, 7l, 7m and 7e to be 1.21, 2.03 and 2.86 mol respectively. This compound 7h causes a significant increase in the number of cells in G0–G1 phase, with a corresponding decrease in the number of cells in S and G2–M phase. It induces tumor cell apoptosis in a dose-dependent manner. While comparing the docking results, we observed that, compound 7h, 7i, 7m, 7e were found to be the most efficient analogues to inhibit EGFR-TKs via creating MET769, ASP831, LYS721 and CYS773 amino acids comparable to Erlotinib. Conclusion: In conclusion, 1,3,5-triazines have shown promising anticancer activity via inhibition EGFR-TK in lung carcinoma and represents a potential therapeutic application in NSCLC.

Keywords: NSCLC, 1,3,5-triazine, EGFR-tyrosine kinase

PUB082 ROLE OF ISOLATED FLAVONOID FROM INDIGOFERA TINCTORIA IN N-NITROSOPYRROLIDINE INDUCED BIOCHEMICAL CHANGES RELATED TO LUNG CANCER
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Background: Lung cancer is a second leading cause of deaths throughout the globe. The key cause, tobacco smoke contains a number of nitrosamines like N-nitrosopyrrolidine (NPPY) interact with cellular system and alter redox signalling pathway. Medicinal plants like Indigofera tinctoria can be a promising source in treatment. The study was endeavor to evaluate the role of isolated compound 3,6-dihydroxy-(3',4',7-trimethoxyphenyl)-chromen-4-one-7-glucose (ITC) in lung cancer related changes. Methods: Lactate dehydrogenase (LDH), Lysosomal parameters: Acid phosphatase (ACP), Type II enzyme: Alkaline phosphatase (ALP), Clara cell marker enzymes: γ-glutamyl transpeptidase (GGT), Glycoproteins: Hexose, Hexosamine and Sialic Acid and total protein content were estimated. Results: LDH, ACP and GGT levels showed augmentation while ALP activity was alleviated in NPPY treated animals, the level of glycoproteins significantly boost up when compared to the values of animals of control group. Total protein content was found to be heightened in the mice bearing lung cancer significantly when compared to the normal healthy group of animals. The post treatment with isolated compound significantly restored the abnormal values of lung cancer biomarkers. In group of NPPY treated animals, the level of glycoproteins significantly boost up when compared to the values of animals of control group. Total protein content was found to be heightened in the mice bearing lung cancer significantly when compared to the normal healthy group of animals. Post treatment with isolated compound significantly restored the abnormal values of lung cancer biomarkers. Conclusion: Study revealed that flavonol isolated from Indigofera tinctoria hydromethanolic extract can alter various endogenous antioxidant enzymes, and lung specific markers significantly and thus can be further used as a promising treatment of pulmonary cancer after drug development.

Keywords: Lung Cancer, Flavonoid, Biochemical parameters, antioxidants

PUB083 NEO-ADJUVANT PLATINUM BASED CHEMOTHERAPY IN LOCALLY ADVANCED THYMIC CARCINOMA
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Background: Thymic carcinoma is a rare malignant tumor. At present, cisplatin based doublet or triplet antitumor drugs are used in neo-adjuvant setting for advanced thymic carcinomas. However, no optimal chemotherapeutic regimen is well established and recent small case studies with carboplatin and paclitaxel doublet demonstrates the similar efficacy with less toxicity. We retrospectively evaluated effectiveness and toxicity of platinum based doublet chemotherapy for patients with thymic carcinomas.

Methods: Between 2001 and 2011, we retrospectively identified 21 patients from hospital information system with pathologically confirmed advanced thymic carcinoma, who were treated with platinum based doublet chemotherapy followed by surgical resection. The most commonly used regimen being carboplatin plus doxetaxel in 85% of the patients. Other regimens included cisplatin plus gemcitabine, carboplatin plus gemcitabine and cisplatin plus doxorubicin plus cyclophosphamide.

Results: The clinical response rate was achieved in 61.5% of the patients. The disease control rate was achieved in 92% of the patients. The median progression-free survival was 20 months (95% CI 1.3-35.5 months) and median OS survival was 55%.

Conclusion: We concluded that platinum doublet chemotherapy is active and tolerable for advanced thymic carcinoma in the front-line setting with regard to efficacy, toxicity, and usage in clinical setting.

Keywords: Platinum, Thymic carcinoma, neoadjuvant

PUB084 LONG TERM SURVIVAL OF STAGE IIIIB NON-SMALL CELL LUNG CANCER (NSCLC) PATIENTS TREATED WITH CONCURRENT CHEMORADIATION
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Background: The optimal treatment strategy for Stage IIIIB NSCLC patients with a T4N1-1 tumor is a matter of debate. In prospective combined modality series including surgery, the median overall survival (OS) is approximately 24 months. We hypothesized that results comparable to regimens including surgery can be achieved with concurrent chemoradiation in this patient group.

Methods: In our retrospectively collected database of NSCLC patients, all patients with T4 (mediastinal invasion) N0-1 NSCLC receiving concurrent chemoradiation were included. One patient had a recurrence after post-operative pneumonectomy. All patients were given 3 cycles chemotherapy (cisplatin and etoposide), radiotherapy (RT) was started at the 2nd course of chemotherapy. OS was calculated from date of diagnosis (Kaplan-Meier method). Toxicity was scored according to CTCAEv3.0. Results: 42 patients (8 female, 34 male) with a median age of 62.5 ± 9 years (44-80 years) were included from January 2005 until December 2009. Stage distribution: 86% T4N0 (n=36), 14% T4N1 (n=6). The maximal tumor dose was 66 Gy using conventional fractionation. The median prescribed mean lung dose was 15 ± 4.4 Gy (5.03-19.9 Gy). Acute toxicity: 1 patient experienced grade 3 dyspnea during RT. Grade 3 dysphagia occurred in 5 patients (12%) during RT requiring tube feeding in 3 of these patients (7%). Dysphagia persisted later than 1 month after RT in 1 patient (2%). Grade 3 dysphagia only occurred in patients treated concurrently. Grade 3 cough occurred in 1 patient during RT, no patient experienced grade 3 cough 1 month after RT. 2 patients died within 3 months after start of RT, one due to myocordial infarction, one of unknown causes. Severe late toxicity was not present: no grade 3 complications more than 3 months after the end of radiotherapy. With a median follow-up of 42 months, the median OS for the whole group is 34 months (95% CI 24-43.3 months). 2-year OS survival is 55 %. Conclusion: Concurrent accelerated chemoradiation using an individualized dose prescription is a valid treatment strategy for stage IIIIB T4N0-1 NSCLC patients yielding very promising OS results with low toxicity.

Keywords: NSCLC, chemoradiation

PUB085 OUTCOMES OF SMALL CELL LUNG CANCER PATIENTS WITH BRAIN METASTASES: PROGNOSTIC FACTORS BASED ON AN ANALYSIS OF 225 CASES
Abstracts

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Background: Brain metastases (BMs) are common in patients with small cell lung cancer (SCLC) and are usually fatal. The purpose of this analysis is to evaluate the outcomes of SCLC patients with BMs and explore the prognostic factors.

Methods: Pathological diagnosis of SCLC patients with radiologically confirmed BMs were enrolled except those who received surgery of primary lesion. Overall Survival(OS) was calculated from the date of diagnosis of BMs to the date of any cause, or the last follow-up. OS was estimated by the Kaplan-Meier method. Univariate and multivariate analyses were performed by the log-rank and Cox’s proportional hazard model test, respectively.

Results: From Jan 2011 to Oct 2014, 224 patients were eligible for the study. The median follow-up time was 14 months(range:1-77). For the entire cohort, median OS was 9 months(95%CI,7.6-10.4), 1- and 2-year OS rate were 31.2% and 7.7%, respectively. As expected, the OS of patients with oligometastatic BMs(≤3) turned out to be significantly better compared to the survival of patients with non-oligometastatic BMs(>3)10 months Vs 7 months, P<0.0001. Similarly, median OS of patients with initial brain metastatic presentation was 11 months(95%CI,9.4-12.6) while OS of patients with brain metastasis development during follow-up was 7 months(95%CI,5.7-8.3), the difference was statistically significant(P=0.021). In addition, patients received radiation to brain or chemotherapy after diagnosis of BMs also had a significantly better survival rate(P<0.001). Multivariate analyses revealed sex, radiation to brain, number of BMs and chemotherapy after diagnosis of BMs were relevant parameters in predicting outcome of SCLC patients with BMs.

Conclusion: In our investigated population, median OS of SCLC patients with BMs was 9 months. Therapy after diagnosis of BMs(radiation to brain or chemotherapy) could improve clinical outcomes. Meanwhile, sex and number of BMs were implicated to have an impact on survival, these may provide stratification factors in predicting prognosis in future.

Keywords: Small cell lung cancer, brain metastases, survival, prognostic factor

PUB087 DOMESTIC COOKING FUEL AS A RISK FACTOR FOR LUNG CANCER IN WOMEN - A CASE CONTROL STUDY

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Background: Tobacco smoking is the most common risk factor for lung cancer. But a significant proportion of lung cancer occurs in non-smokers. Indoor pollution due to domestic fuels has been recently implicated as a causative agent in lung cancer especially in women. We conducted a case control study to find out the role of Domestic Cooking Fuel as a risk factor for Lung Cancer in Indian women. Methods: A case control study 67 women with proven lung cancer were recruited. Forty-six females having a non-malignant respiratory disease constituted the control group. The patients and controls were asked about the exposure in various cooking fuels using a questionnaire. Results: There were 50(74.6%) non-smokers and 17(25.4%) smokers among the female lung cancer cases (p=0.016). Adenocarcinoma was the commonest histological type of malignancy (n=26, 38.8%) in the whole group and was the predominant disease in the non-smoking females. Tobacco smoking was the most important risk factor for lung cancer with OR of 4.87 (95% CI 1.34-17.76). Among non-smokers, pure biomass fuel was associated with a lesser risk (OR=0.3, 95% CI 0.04-1.82). Conclusion: This study indicated that domestic cooking fuel exposure is an important risk factor in the causation of lung cancer among women in addition of exposure to tobacco smoke.

Keywords: Women, domestic cooking fuel, lung cancer

PUB086 CONCURRENT LOSS OF TUMOUR SUPPRESSORS LKB1 AND BRG1 CONTRIBUTE TO EPIGENETIC DYSREGULATION IN NSCLC

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Background: Lung cancer is the leading cause of cancer-related death in men and women worldwide. Symptoms of lung cancer do not usually present themselves until the disease is at an advanced stage, where traditional methods are generally ineffective. Therefore, there exists a need to identify proteins and biomarkers for earlier detection. LKB1 is a multitasking tumour suppressor kinase that regulates many biological processes including cell metabolism, the immune system and is found mutated in 40% of NSCLC. BRG1 is another tumour suppressor found mutated in 35% of NSCLC and is involved in chromatin remodelling and epigenetic regulation; epigenetic dysregulation has been well regarded in altering gene expression and contributes to genomic instability and cancer progression. Interestingly, LKB1 binds to and interacts with BRG1, both are located in close chromosomal proximity and are found mutated together in NSCLC. Given that BRG1 is involved in epigenetic regulation and LKB1 interacts with BRG1, distinct global histone modification changes may serve as predictive biomarkers when both tumour suppressors are lost in NSCLC. Methods: Human NSCLC cell lines which differ in expression of LKB1 and BRG1 were used: H1299 (LKB1+/BRG1+), H460 (LKB1-/BRG1+), A549 (LKB1-/BRG1+), and Calu-3 (LKB1-/BRG1-). The LKB1/BRG1 expression profile was confirmed for each cell line by western blot analysis. Cell lines were screened for differences in expression of various global H3 and H4 acetylation, methylation and phosphorylation modification patterns by western blot analysis. Results: The majority of screened global H3 and H4 acetylation, phosphorylation and methylation modifications displayed a reduced expression when tumour suppressors LKB1 and BRG1 were concurrently lost. A dramatic decrease in global H4K20me3 expression, typically associated with transcriptional repression was observed in the double negative A549 cell line. Conclusion: These findings suggest that distinct histone modification changes occur when LKB1 and BRG1 are concurrently lost in NSCLC. Taken together, screening for epigenetic histone changes may help to serve as a predictive biomarker in this subset of NSCLC.

Keywords: BRG1, NSCLC, LKB1, histone modification

PUB088 ERLOTINIB IN SECOND LINE TREATMENT OF METASTATIC LUNG CANCER: ABOUT 20 CASE OF NON-SMALL CELL LUNG

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Background: Primary lung cancer is the most common male cancer and is the leading cause of cancer death in the world. The prognosis is poor despite active progress of therapy (the arrival of 1,2,3 generation TKI, and immunotherapy). 45% of NSCLC are metastatic, cisplatin associated with third generation drug (gemcitabine, pemetrexed) remains the standard in the treatment of first line metastatic in NSCLC. The ERLOTINIB has shown efficacy in the first-line in metastatic EGFR mutated NSCLC chemo naive and second-line metastatic with unknown EGFR status. The aim of the study is the evaluation of progression-free survival (PFS), overall survival (OS) and to assess toxicity of ERLOTINIB in second line setting. Methods: A retrospective
study including 20 patients with NSCL stage IV. All patients received Erlotinib 150 mg/day continuously in second line setting after failure of platinum based chemotherapy, associated with pemetrexed for non squamous cell carcinoma and associated with gemcitabine for squamous cell carcinoma (scC).

**Results:** Twenty patients was included in the study; the average age was 60 years with male predominance (19 men and one woman), PS ranges from 0 to 3 (50% has PS 0-1, and 38% PS 2, 12 to 3%). Histological type predominant is adenocarcinoma (60%) treated in first line with Cisplatin + Pemetrexed; 40% squamous cell carcinoma type of cases treated with platine + Gemcitabine. PFS was 5 months with 12 months of overall survival. The most common side effects was: 50 % skin rash of the face (50%) with 10 % of grade III, 20 % of Diarrhea grade II.**Conclusion:** Erlotinib is well tolerated as second line treatment of metastatic NSCLC with unknown EGFR status. This second line treatment with erlotinib show an encouraging median survival and PFS in this setting.

**Keywords:** second line treatment, EGFR unknow, NSCLC, Erlotinib

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**PUB089 TISSUE ENGINEERED CLINICAL AIRWAY RECONSTRUCTION FOR LUNG CANCER TREATMENT**

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**Background:** Delayed revascularization process and substitute infection remain key challenges to tissue engineered TE airway reconstruction. We advanced an “in-vivo bioreactor” design described as implanted TE substitutes perfused with an intra-scaffold medium flow created by an extracorporeal portable pump system for in situ regeneration. The perfusate will maintain the survival of pre-seeded cells secreting revascularization growth factors to accelerate revascularization process. Meanwhile antibiotic inside the perfusate will control topical infection. **Methods:** One stage IIIA squamous lung cancer patient received a 5cm TE airway substitute with in-vivo bioreactor design to bridge left basal segment bronchus to carina avoiding left pneumonectomy. Intra-scaffold continuous Ringer’s-Gentamicin perfusion together with orthotopic peripheral total nuclear cells TNCs injection twice a week lasted for one month. The perfusate waste were collected very 4 hours for revascularization growth factors test. **Results:** The patient recovered uneventfully. Bronchoscopy follow-up showed revascularization and reepithelialization were confirmed four months postoperatively. Perfusate waste test demonstrated various revascularization growth factors secreted by TNCs. The patient received two cycles of chemotherapy and 30Gy radiotherapy thereafter without complications related to the TE substitute.

**Conclusion:** In-vivo bioractor combines the traditionally separated in vitro 3D cell-scaffold culture system and the in vivo regenerative processes associated with TE substitutes, while treating the recipients as bioreactors for their TE prostheses. This design is feasible to be used in clinic. We also proved for the first time that TE airway substitute is able to tolerate chemo-radiotherapy and suitable to be used in cancer treatment.

**Keywords:** tissue engineering, airway reconstruction, lung cancer surgery

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**PUB090 IDENTIFICATION OF A NOVEL APPROACH TO PHOSPHORYLATE IRF3 AND ITS ENGAGEMENT TO INDUCE APOPTOSIS VIA MDAS/RIG-I PATHWAY IN NON-SMALL CELL LUNG CANCER**
Background: Immuno therapy for lung cancer is increasingly being contemplated as the most effective manners to counteract this malignancy in the future. The RIG-I-like receptors (RLRs) melanoma differentiation-associated protein 5 (MDA5) and retinoic acid-inducible gene 1 (RIG-I) are indispensable receptors for recognizing pathogen-associated molecular patterns (PAMPs), and interferon regulatory factor 3 (IRF3) endows the potentiality of inciting innate immunity in cancers. However, the roles of IRF3 in innate immunity of lung cancer are deeply obscure. Methods: We collected fresh excised small cell lung cancer samples/adjacent tissues and transfected IRF3, MDA5/IRF1 by quantitative PCR(q-PCR) and Western Blot. Then non-small cell lung cancer (NSCLC) cell lines A549,H1299 were transfected with Poly(I:C), investigating the innate immunity activity and apoptosis by q-PCR, Western Blot, ELISA, and flow cytometry. Small interfering RNA(siRNA) and plasmid siRNA experiments were employed to knocked down MDA5/ RIG-I and IRF3 respectively. Simultaneously, we constructed recombinant plasmid to over express IRF3 in A549,H1299 cell lines. Results: In this study, we found that the expression of MDA5/RIG-1/IRF3 in NSCLC tissues were significantly higher than the corresponding adjacent tissues. In vitro, innate immunity pathway was triggered predominantly when transfecting the NSCLC cell lines A549,H1299 with Poly(I:C) independent direct addition to culture medium, accompanying the phosphorylation of Ribosomal protein S6 kinase (S6K) and IRF3 in 30 minute, treatment with TBK1 inhibitor BX795 sharply decreased p-S6K, as a consequence of shrinkage of p-IRF3. In line, when p-S6K was inhibited by mTOR inhibitor Rapamycin, the variance of p-S6K and p-IRF3 resembled the effects of BX795, leading to the impairment of innate immunity. Furthermore, knockdown of MDA5/IRG-I with siRNA can dampen the phosphorylation of S6K and IRF3, the degree of innate immunity and the apoptosis induced by Poly(I:C). In addition, downregulation of IRF3 hindered the innate immunity and the activation of caspase3, caspase8. Conversely, overexpression of IRF3 promoted the expression of TRAIL and further activated the apoptotic signaling pathway. Conclusion: These results suggested that p-S6K under the control of MDA5/RIG-I regulated the apoptosis induced by Poly(I:C). In addition, downregulation of IRF3 sharply decreased p-S6K, as a consequence of shrinkage of p-IRF3. In line, when p-S6K was inhibited by mTOR inhibitor Rapamycin, the variance of p-S6K and p-IRF3 resembled the effects of BX795, leading to the impairment of innate immunity. Furthermore, knockdown of MDA5/IRG-I with siRNA can dampen the phosphorylation of S6K and IRF3, the degree of innate immunity and the apoptosis induced by Poly(I:C). In addition, downregulation of IRF3 hindered the innate immunity and the activation of caspase3, caspase8. Conversely, overexpression of IRF3 promoted the expression of TRAIL and further activated the apoptotic signaling pathway. Conclusion: These results suggested that p-S6K under the control of MDA5/RIG-I regulated the apoptosis induced by Poly(I:C). In addition, downregulation of IRF3 sharply decreased p-S6K, as a consequence of shrinkage of p-IRF3. In line, when p-S6K was inhibited by mTOR inhibitor Rapamycin, the variance of p-S6K and p-IRF3 resembled the effects of BX795, leading to the impairment of innate immunity. Furthermore, knockdown of MDA5/IRG-I with siRNA can dampen the phosphorylation of S6K and IRF3, the degree of innate immunity and the apoptosis induced by Poly(I:C). In addition, downregulation of IRF3 hindered the innate immunity and the activation of caspase3, caspase8.

Keywords: IRF3, Innate immunity, apoptosis, MDA5/IRG-I

**PUB091 METABOLIC AND EPIGENETIC CHANGES ASSOCIATED WITH LUNG CANCER USING A CRISPR/CAS9 MOUSE MODEL**

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Background: In NSCLC, loss-of-function (LOF) mutations are found in tumour suppressors, highlighting the importance of these genes in the aetiology of lung cancer. The major tumour suppressors (TS) associated with the development of lung cancer are p53 and the kinase LKB1. Unlike these genes that have been successfully exploited therapeutically, LOF alterations in TS are difficult to exploit therapeutically. The goal of our research is to understand how the loss of TS function allows for metabolic and epigenetic adaptation that favour conditions for tumour growth. Methods: We developed a CRISPR/Cas9 mouse model of lung cancer representative of tumour suppressors lost in NSCLC that has allowed us to evaluate the role metabolism and epigenetics plays in supporting tumour growth. Since LKB1 and p53 are the most common LOF tumour suppressors found in NSCLC, and Kras is the most commonly abundant of oncogene, using the Cre-dependent Cas9 mouse model developed by the Zhang Lab at the Broad Institute, will allow us to characterize CRISPR developed lung cancers at a molecular level. Mice were treated by inhalation with CRISPR-directed viruses that target the excision of Lkb1, p53 and activation of Kras compared to mice treated with control virus. Post-treatment, circulating blood was collected weekly and lungs were harvested at the end of the study. Harvested lungs were analyzed for metabolic epigenetic profile, while epigenetic profiles were conducted on harvested blood. Results: Lung tumours and circulating blood were harvested from mice, followed by analysis of global epigenetic modifications, and for metabolic expression. The metabolic profile of lung tumours harvested from CRISPR/Cas9 mice that lack expression of Lkb1, p53 and express enhanced Kras, was significantly different from the metabolic profile of lungs harvested from control mice, favouring a switch from glycolysis to mitochondrial metabolism. Acetylation and methylation modifications to histones 3 (H3) and H4 were significantly different compared to control mice, as was the macrophage activation profiles. Conclusion: The goal of our study was to 1) identify and characterize aberrant metabolic and epigenetic processes that allow for cancer adaptation and 2) develop non-invasive liquid biopsy that would provide rapid and affordable early diagnostic tool in clinic. We conclude from our study that patients with lung cancers that lack expression of Lkb1 are likely to respond favourably to interventions that simultaneously target aberrant metabolism with modifiers of tumour epigenetic landscape. Our findings suggest that loss of Lkb1 expression serves as a marker for lung cancers that are metabolically and epigenetically challenged.

Keywords: NSCLC, LKB1, CRISPR/Cas9 mouse model

**PUB092 EFFICACY OF CRIZOTINIB AND Pemetrexed-based Chemotherapy in Chinese NSCLC Patients with ROS1 Rearrangement**

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Background: ROS1 rearrangement is a novel molecular subgroup of non-small-cell lung cancer (NSCLC). This study aimed to investigate the efficacy of crizotinib and pemetrexed-based chemotherapy in Chinese NSCLC patients with ROS1 rearrangement. Methods: We retrospectively identified patients with NSCLC who were screened for ROS1 fusion using multiplex reverse transcription-polymerase chain reaction (RT-PCR) from October 2013 to February 2016. The thymidylate synthase (TS) mRNA levels were tested using quantitative real-time RT-PCR. Results: A total of 2309 patients received ROS1 fusion detection and 512 (2.2%) patients had ROS1 rearrangement. There was no significant difference between ROS1 fusion-positive and fusion-negative cohorts in demographic data. For all patients, crizotinib-treated group had a higher overall response rate (ORR, 80.0%), disease control rate (DCR, 90.0%) and longer progression-free survival (PFS, 294 days) compared with the rates in pemetrexed-treated group (ORR, 40.8%; DCR, 71.4%; PFS, 179 days) and non-pemetrexed-treated group (ORR, 25.0%; DCR, 47.7%; PFS, 110 days). ORR, DCR and PFS were similar in three major ROS1 fusion patterns. For first-line treatment, patients received pemetrexed had significant longer PFS than those received non-pemetrexed chemotherapy (209 vs. 146 days, P = 0.0107). In pemetrexed-treated cohorts, ROS1-positive patients with low TS expression had statistically significant longer PFS than those with high TS expression (184 vs. 110 days, P = 0.0105). Conclusion: Crizotinib was also highly active at treating Chinese NSCLC patients with ROS1 rearrangement. TS expression could predict the efficacy of pemetrexed-based therapy in ROS1 fusion-positive patients.

Keywords: Non-small-cell lung cancer, ROS1 rearrangement, crizotinib, pemetrexed
Abstracts

PUB094 CORRELATION OF CLINICOPATHOLOGIC FEATURES AND LUNG SQUAMOUS CELL CARCINOMA SUBTYPES ACCORDING TO THE 2015 WHO CLASSIFICATION

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Shanghai Lung Cancer Center, Shanghai Chest Hospital, Shanghai/China

Background: This study aimed to determine the relationship between clinicopathologic features and lung squamous cell carcinoma subtypes according to the 2015 WHO classification. Methods: We identified 368 operable lung squamous cell carcinoma patients who had undergone a complete surgical resection at Shanghai Chest Hospital between April 2015 and March 2016. Results: Among all patients, the percentages of lung squamous cell carcinoma subtypes were: 68.5% (252/368), 26.2% (97/368), and 5.1% (19/368) for keratinizing squamous cell carcinoma(KSCC), nonkeratinizing squamous cell carcinoma(NKSCC), and basaloid squamous cell carcinoma(BSCC), respectively. There were more smokers in patients with KSCC than in patients with other subtypes (p=0.004). There were no significant relationships between pathological subtypes and other clinicopathologic features, such as gender, age, location type, type of resection, stage, visceral pleural involvement, lymphovascular invasion, and lymph node involvement. The expressions of P40, CK5/6, TTF-1, Napsin A, and CK7 were also not significantly different in three subtypes. Conclusion: Our study revealed that there were no significant relationships between clinicopathologic features and lung squamous cell carcinoma subtypes.

Keywords: Lung Squamous cell carcinoma, pathological subtype, clinicopathologic feature

PUB095 COMPUTED TOMOGRAPHY IMAGING OF SUPERIOR VENA CAVA INVOLVEMENT IN T4-CLASSIFIED LUNG CANCER

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1Abderahmen Mami Hospital, Ariana/Tunisia, 2Oncology, Abderahmen Mami Hospital, Ariana/Tunisia

Background: Superior vena cava (SVC) can be involved in many ways in patients with lung cancer. This latter is considered to be the most frequent cause of SVC syndrome which is a medical emergency requiring prompt evaluation and treatment. The SVC syndrome can reveal the disease or can be discovered on computed tomography (CT) of the chest. The objectives of our study are to specify CT characteristics of SVC involvement in T4-classified lung cancer and to estimate the frequency of its total obstruction in this patients category. Methods: We retrospectively reviewed of CT scans of 177 consecutive patients with T4-classified lung cancer, newly and fully diagnosed in our institution during the year 2015. All CT examinations were performed after contrast agent administration. Only patients with mediastinal involvement were retained. Every aspect of SVC involvement was noticed separately. Results: Among the 177 patients, mediastinal invasion was observed in 132 cases (74.5%). SVC was involved in 32 cases (24%). Lung cancer was located on the right side in 91% of cases. The involvement included: - A contact with the tumor with loss of the fat layer (n=7). - An inclusion of the vessel in the tumoral mass with narrowing of the lumen (n=17). - An intraluminal tumoral bud (n=8). - A complete obliteration (n=6). Collateral venous circulation was observed in 8 cases. Adenocarcinoma and small cell lung cancer were the most frequent histological types responsible for SVC obstruction. Clinical signs of SVC syndrome were obvious in only 6 patients. Conclusion: Superior vena cava involvement is quite frequent in advanced stage of lung cancer. However, the total tumoral obstruction of this vessel is rare. CT helps defining the mechanism and the severity of the SVC involvement.

Keywords: superior vena vava, lung cancer, Advanced stage

PUB097 ENHANCED DELIVERY OF ANTICANCER DRUG TO THE LUNGS VIA LIPOSONAL AEROSOLS

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1Manav Bharti University, Kanpur/India, 2Icfai University, Kanpur/India

Background: Lung cancer tends to spread very early, and is a very life threatening cancer and one of the most difficult cancers to treat. Non-small cell lung cancer (NSCLC) usually spreads and grows more slowly than small cell lung cancer. There are three forms of NSCLC: Adenocarcinomas are found in an outer area of the lung. Squamous cell carcinomas are usually found in the center of the lung by an air tube (bronchus). Large cell carcinomas can occur in any part of the lung. Liposomes were used as Effective encapsulation of both hydrophobic & hydrophilic molecules. Due to their ability to solubilize poorly water soluble drugs, facilitate their nebulization, minimizing clinical drug dose and reducing toxicity, prolonging and targeting release of therapeutic agents by modification of liposome surface. Methods: The failures of the present delivery systems are – Oral administration of etoposide at varying dosage for the treatment of lung cancer causes GI toxicity and disturbances of liver function. The parenteral administration of etoposide for lung cancer treatment has been reported to cause severe hepatic impairment and Hypotension. Moreover, intravenously injected ligands mediated liposomes have been limited due to- Leakage of their contents before they reach the target tissue, Rapid clearance from the blood stream, uptake by the macrophages of liver and spleen. Results: Liposomes were prepared by lipid cast film method, optimized and then coupled with Mannose. Drug loaded Liposomes were characterized in-vitro for shape, size, and stability in various body fluids. The Air-jet nebulizer system was used for aerosol and was characterized for Appearance, Leak Test, Internal Pressure, Amount discharge/actuation, Spray Pattern area and Penetration Efficiency. The in-vitro study comprised of estimation of serum and tissue distribution of drug and fluorescence microscopy. Conclusion: Liposomes formed were multimellar and were found to be stable in gastric and intestinal fluids. Fluorescence microscopy suggested that liposomes were taken up by the gut associated lymphoid tissues and therapeutic level of drug can be achieved at desired site. Thus, from the results obtained it can be concluded that the Aerosolized mannose liposomes can deliver drug to the cancerous cells in an effective way and hold great potential for lung targeting. Through mannosylated liposomes, therapeutic level of drug can be achieved at desired site. The system carried dual function, firstly retention of drug and secondly selective delivery of etoposide to lungs.

Keywords: etoposide, Aerosols, liposomes

PUB097 CORRELATION OF CLINICOPATHOLOGIC FEATURES AND LUNG SQUAMOUS CELL CARCINOMA SUBTYPES ACCORDING TO THE 2015 WHO CLASSIFICATION

Gomed Agarwal1, Saurabh Bhargava1, Vishal Bhargava1
1Guru Teg Bahadur Hospital, Kanpur/India, 2Manav Bharti University, Kanpur/India

Background: Cancer is uncontrollable growth of cells which are devoid of apoptosis. We developed a novel strategy ie Ligand mediated tumor targeting via carrier systems. Multiwalled Carbon nanotubes (MWCNTs) were used as it directly enters into the cell without passing through endo-lysosomes, large inner volume, distinct inner and outer surfaces & have ability to enter the cell by spontaneous mechanism. Thus, proposed work envisages Rhodamine-123 conjugated Paclitaxel loaded functionalized-CNTs to provide enhanced cell permeation in order to enhance mitochondrial availability of Paclitaxel. Methods: The raw MWCNT were procureed and purified, oxidized & then conjugated with rhodamine-123 by carbodiimide method. The MWCNT’s were characterized in-vitro for shape & size by Scanning(SEM) & Transmission Electron Microscopy(TEM), FTIR analysis, X-ray diffraction and zeta potential determined. Stability studies were performed at exaggerated conditions along with Hemolytic Toxicity Study. The Cell Cytotoxicity Study-MTT Assay was done using Hela cell lines. Mitochondrial localization was determined by CLSM study. The in-vivo part of the study comprised of determining the distribution of drug in various organs by fluorescence microscopy. Results: The Rhodamine-123 conjugated MWCNTs were prepared and characterized. The CNTs showed high paclitaxel loading, sustained release, and excellent biocompatibility as evident by in-vitro drug release and low hemolytic toxicity. Moreover, intravenously injected liposome mediated liposomes, therapeutic level of drug can be achieved at desired site. Conclusion: Thus, Rhodamine-123 conjugated Paclitaxel loaded CNTs system have potential to provide an enhanced cell permeation and mitochondrial localization for effective tumour chemotherapy.

Keywords: paclitaxel, CNT

PUB098 PANIC DISORDER AND DYSPNEA IN PATIENTS WITH LUNG CANCER IN A NIGERIAN DEPENDENT UNIT

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Background: The objectives of this study were to determine the prevalence and dyspnea and panic disorder in patients with lung cancer in a teaching hospital and also do determine the association between them. Methods: This study comprised of estimation of serum and tissue distribution of drug and fluorescence microscopy. Conclusion: Liposomes formed were multimellar and were found to be stable in gastric and intestinal fluids. Fluorescence microscopy suggested that liposomes were taken up by the gut associated lymphoid tissues and therapeutic level of drug can be achieved at desired site. Thus, from the results obtained it can be concluded that the Aerosolized mannose liposomes can deliver drug to the cancerous cells in an effective way and hold great potential for lung targeting. Through mannosylated liposomes, therapeutic level of drug can be achieved at desired site. The system carried dual function, firstly retention of drug and secondly selective delivery of etoposide to lungs.

Keywords: etoposide, Aerosols, liposomes

PUB097 CARBON NANOTUBES FOR EFFICIENT MITOCONDRIAL TUMOR TARGETING

Gomed Agarwal1, Saurabh Bhargava1, Vishal Bhargava1
1Guru Teg Bahadur Hospital, Kanpur/India, 2Manav Bharti University, Kanpur/India

Background: Cancer is uncontrollable growth of cells which are devoid of apoptosis. We developed a novel strategy ie Ligand mediated tumor targeting via carrier systems. Multiwalled Carbon nanotubes (MWCNTs) were used as it directly enters into the cell without passing through endo-lysosomes, large inner volume, distinct inner and outer surfaces & have ability to enter the cell by spontaneous mechanism. Thus, proposed work envisages Rhodamine-123 conjugated Paclitaxel loaded functionalized-CNTs to provide enhanced cell permeation in order to enhance mitochondrial availability of Paclitaxel. Methods: The raw MWCNT were procureed and purified, oxidized & then conjugated with rhodamine-123 by carbodiimide method. The MWCNT’s were characterized in-vitro for shape & size by Scanning(SEM) & Transmission Electron Microscopy(TEM), FTIR analysis, X-ray diffraction and zeta potential determined. Stability studies were performed at exaggerated conditions along with Hemolytic Toxicity Study. The Cell Cytotoxicity Study-MTT Assay was done using Hela cell lines. Mitochondrial localization was determined by CLSM study. The in-vivo part of the study comprised of determining the distribution of drug in various organs by fluorescence microscopy. Results: The Rhodamine-123 conjugated MWCNTs were prepared and characterized. The CNTs showed high paclitaxel loading, sustained release, and excellent biocompatibility as evident by in-vitro drug release and low hemolytic toxicity. Moreover, intravenously injected liposome mediated liposomes, therapeutic level of drug can be achieved at desired site. Conclusion: Thus, Rhodamine-123 conjugated Paclitaxel loaded CNTs system have potential to provide an enhanced cell permeation and mitochondrial localization for effective tumour chemotherapy.

Keywords: paclitaxel, CNT
We compared 80 patients with lung cancer who attended the de-addiction unit of a Nigerian Private Psychiatric Hospital between January 2009 and December 2013 for tobacco cessation. Patients were in stage I-IV non-small cell lung cancer. Measures: The Mini International Neuropsychiatry Interview (MINI); was used to obtain the prevalence of Panic disorder. Dyspnoea was determined by self-reports. Disability was assessed using the 12 item World Health Organization Disability Assessment Schedule. Ethical Consideration: Ethical approval and consent were obtained.

### Results

<table>
<thead>
<tr>
<th>Demographic Characteristics of the Case and Control Groups</th>
<th>Case</th>
<th>Control</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td><strong>Sociodemographic</strong></td>
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<td></td>
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<tr>
<td><strong>N = 80</strong></td>
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<tr>
<td><strong>Age</strong></td>
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<tr>
<td>Mean (SD)</td>
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<td>41.34</td>
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<tr>
<td>Female</td>
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<tr>
<td><strong>Years of Education</strong></td>
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<tr>
<td>&lt; 12</td>
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<td>7-12</td>
<td>32</td>
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<tr>
<td>&lt; 12</td>
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<td>8.8</td>
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<tr>
<td><strong>Dyspnoea</strong></td>
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<tr>
<td><strong>Panic Disorder</strong></td>
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</tr>
<tr>
<td>N = 12</td>
<td>N = 68</td>
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<tr>
<td><strong>Stage of Disease</strong></td>
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<tr>
<td>1 &amp; 2 (n%)</td>
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<tr>
<td>3 to 5 (n%)</td>
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</table>

### Discussion

The Mini International Neuropsychiatry Interview (MINI) was used to obtain the prevalence of Panic disorder. Dyspnoea was determined by self-reports. Disability was assessed using the 12 item World Health Organization Disability Assessment Schedule. Ethical Consideration: Ethical approval and consent were obtained.

### Conclusion

### Keywords

Consultation Liaison Mental Health, lung cancer, dyspnoea, Panic Disorder

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14/44 (26.8%) patients with dyspnea had panic disorder 3/26 (13%) patients with no dyspnea had panic attack, FE = 0.01. **Conclusion:** In the current sample, over half of patients reported dyspnea. Patients who reported dyspnea were more likely to have had panic disorder. This study highlights the need for consultative liaison mental health services in patients living with lung cancer.

### Keywords

Consultation Liaison Mental Health, lung cancer, dyspnoea, Panic Disorder
1x osimertinib, CR: 1x osimertinib). Median PFS on first EGFR-TKI was 4.5 months (range: 3.7-9 months). Two of five pts responded to platinum-based chemotherapy (median PFS: 5.5 months [range: 0.25-10 months]). Conclusion: De novo concurrent ALK/KRAS alterations are associated with resistance to ALK-TKI treatment in seven out of eight pts, although one patient achieved ongoing disease stabilization for 26 months. Thus, platinum-based chemotherapy should be 1L treatment for these patients. In ALK/EGFR pts outcomes with ALK and EGFR-TKI seem inferior to what would be expected in pts with either alteration. EGFR-TKIs may potentially be more active compared to ALK-TKIs in ALK/EGFR pts. Worse outcomes to ALK-TKI may partly be related to false-positive ALK test results. Further studies are needed to clarify which patients may still benefit from the respective TKI.

Keywords: KRAS, EGFR, Co-Mutations, ALK

**PUB101 HIGH PREDICTIVE VALUE OF INVASIVENESS FOR IPAS FROM PREINVASIVE LESIONS APPEARING AS PURE GROUND-GLASS NODULES ON ULTRA-HIGH RESOLUTION CT**

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Department of Radiotherapy, Shanghai Chest Hospital, Shanghai/China, Shanghai Pulmonary Hospital, Shanghai/China

**Background:** To analyse the correlations between histological invasiveness and radiological pulmonary adenocarcinomas (IPAs) and preinvasive lesions appearing as pure ground-glass nodules on Ultra-HRCT. To evaluate the potential predictive factors of invasiveness for pure ground-glass nodules (PGGN) on Ultra-HRCT.

**Methods:** Retrospective analysis of 123 lesions (16 were Atypical adenomatous hyperplasia (AAH), 35 were Adenocarcinoma in situ (AIS), 37 were Invasive adenocarcinoma (IA)) with PGGN on Ultra-HRCT from January 2014 to June 2014 in a single-central hospital. Only one lesion can be enrolled in every patient. There were 93 females and 30 males, with a median age of 58 (24-77) years old. All focuses were resected and confirmed by pathology. The clinical data (gender, age) and Ultra-HRCT findings (lobulation, spiculation, pleural indentation, ateral gathering, bubbles/air bronchogram, shape margin internal uniformity and tumor-lung interface, size of lesion, average density of lesion, the corresponding lung’s average background density) were recorded, pathological data of the 123 cases according to the new lung adenocarcinoma classification proposed by the IASLC/ATS/ERS were recorded. Results: With respect to the correlation between histological invasiveness and the morphological features of PGGN, only tumor-lung interface (P = 0.05) had no correlation with histological invasiveness, and its predictability was quite low (Lambda value, = 0.0). The rest of the morphological features, including lobulation, spiculation, pleural indentation, ateral gathering, bubbles/air bronchogram, shape margin, and internal uniformity were specific factors that differentiated invasive adenocarcinoma from AIS or AAH (P < 0.05). The speculation and internal uniformity showed a good correlation and predictability with the Lambda value (cross-validated correlation coefficient) of 0.519 and 0.568, the odds risk area covered and the position of the picture on cigarette packets needs to be increased.

**Keywords:** Lung adenocarcinoma, high-resolution computed tomography, ground glass nodule, diagnosis

**PUB102 SMOKING HABITS AND AWARENESS ABOUT ANTI-SMOKING ACTS AMONG GENERAL PUBLIC IN GURGAON, HARYANA, INDIA**

Clement Joy Kingsly Francis
Finance and Economy, Nestle India Private Limited, Gurgaon/India

**Background:** India is the world’s third largest tobacco-growing country. The Indian scenario as far as tobacco consumption is concerned is far worse because of the prevalence of the tobacco chewing habit which covers wide spectrum of socioeconomic and ethnic groups and is spread over urbanized area as well as remote village. Tobacco use is alarming in terms of its current and projected future impact on global mortality. Recent shift in global tobacco consumption to developing countries indicate that an estimated 930 million of the world’s 1.1 billion in India alone. Despite the facts, the harmful effects of tobacco chewing and smoking are widely known, many young people start smoking during adolescence, largely because they believe that smoking will boost their social acceptability and image. This study was contemplated with an aim to assess tobacco/smoking habits and awareness about anti-smoking act among general public in Gurgaon, Haryana, India.

**Methods:** A structured questionnaire consisting of 14 questions related to tobacco smoking habits and awareness about anti-smoking act were asked to general public and their response was recorded. Random sampling method was used and data was collected from a cross-sectional survey. Anti-tobacco counselling was given on the spot and followed.

**Results:** The study population consisted of total 430 individuals, male 364 (84.65%) and females 66 (15.34%). Then the questionnaires were asked and statistically analyzed. Around 286 (78.57%) from 364 male were indulged in some form of tobacco usage (smoker = 32.86%, tobacco chewer = 16.78%, both = 11.18%, alcohol + tobacco user = 21.67%). In the present study, most common cause of tobacco usage was pleasure, inducing factor were friends 53.1% followed by parents and siblings. 36.20% patients used tobacco as second hand exposure in job places. 54.8% were aware about the anti-smoking act in public places, so only 6.8% people from all males enrolled, were smoking in public places.

**Conclusion:** Despite the facts, that the harmful effects of tobacco chewing and smoking is widely known, many young people start smoking during adolescence, largely because they believe that smoking will boost their social acceptability and image.

**Keywords:** Tobacco chewing, smoking, anti-smoking act, prevalence.

**PUB103 ROLE OF PICTORIAL WARNING ON CIGARETTE PACKETS IN TOBACCO CESSION - A QUESTIONNAIRE SURVEY AMONG CIGARETTE SMOKERS IN CHENNAI**

Clement Joy Kingsly Francis
Finance and Economy, Nestle India Private Limited, Gurgaon/India

**Background:** Warning labels on cigarette packages are meant to communicate such smoking-associated risks. The study is designed to find out the effectiveness of pictorial warnings present on cigarette packets in India for tobacco cessation among cigarette smokers.

**Methods:** A questionnaire was distributed to 800 current smokers attending and at the department of a college. Statistical analysis was done to find association between socioeconomic status and effectiveness of pictures to quit cigarette smoking.

**Results:** 48% smokers perceive text warning is an efficient method to create awareness, 56% emphasized the importance of pictorial warning and greater area to be covered. 43% felt that warning on cigarette packets helped them to quit smoking.**Conclusion:** Though pictorial warning is an effective method to improve the awareness among smokers on the ill effects of smoking, the size, area covered and the position of the picture on cigarette packets needs to be reviewed to improve the quit rate.

**Keywords:** pictorial warning, cigarettes

**PUB104 AN ASSESSMENT OF ORAL HEALTH STATUS, TOBACCO USE AND CANCER AWARENESS AMONG TEA PLANTATION WORKERS, NILGIRI HILLS, TAMILNADU INDIA**

Clement Joy Kingsly Francis
Finance and Economy, Nestle India Private Limited, Gurgaon/India

**Background:** Tea is an important agro-industry of India, which contributes immensely to the countries economy. Tea garden population constitutes approximately 1/32th of the growing state’s population. Poor socio-economic conditions, ignorance due to illiteracy, over-crowded and unhygienic living conditions in the residential colonies make tea garden population vulnerable to various communicable diseases and malnutrition.

Hence this study was contemplated with an aim to assess the oral health status, tobacco use and cancer awareness among tea plantation workers, Nilgiri Hills, Tamil Nadu, India.

**Methods:** A cross-sectional descriptive study was conducted to assess the tobacco use and cancer awareness among tea plantation workers, Nilgiri Hills. Data was collected using a pretested Questionnaire, which included Demographic data, tobacco habits, its frequency and form. The data collected was analysed using SPSS version 15.
Results: Results showed that among 900 study population, showed 57% had no formal education, 34.5% had not visited dentist before. 64.5% had indigenous brushing habits. A very high prevalence of periodontal disease, tobacco chewing, deep rooted beliefs and customs regarding dentition and dental treatment was observed in this community. Prevalence of oral mucosal lesions in the study population was due to tobacco usage and lack of awareness regarding the deleterious effects of the products used. Conclusion: The dangers from smoking and chewing tobacco are well documented within the literature but the public’s lack of knowledge of the risks is a concern. Health professionals are encouraged to ensure that the public is made aware of these risks, especially those within high-risk groups.

Keywords: Tribes, Tobacco usage, oral health status, WHO oral health proforma, Beliefs.

PUB105 HYBRID-CAPTURE BASED COMPREHENSIVE GENOMIC PROFILING DETECTS EGFR POINT MUTATIONS IN >20% OF PATIENTS MISSED BY STANDARD OF CARE TESTING

James Suh, Alexa Schrock, Adrienne Johnson, Doron Lipson, Laurie Gay, Shakti Ramkisson, Jo-Anne Vergilio, Julia Elvin, Abdur Shakhi, Jeffrey Roys, Philip Stephens, Vincent Miller, Sira Al

Background: In a recent study of 6832 consecutive cases of select NSCLC histologies (specified below), hybrid-capture based comprehensive genomic profiling (CGP) identified 1342 patients (20%) who harbored at least one of 98 distinct genomic alterations (GA) involving EGFR (Suh et al, Oncologist 2016; 21(6): 684-91). In addition, CGP detected EGFR exon 19 deletions in 1777 (22%) of patients who previously tested negative by standard of care (SOC) testing (Schrock et al, Clin. Cancer Res 2016; 22(13): 3281-5). Our aim is to compare the detection rates of CGP versus SOC testing for well-characterized sensitizing EGFR point mutations (pm) in the 6832 patient cohort. Methods: DNA was extracted from 40 microns of FFPE sections from 6832 consecutive cases of lung adenocarcinoma, adenosquamous carcinoma, non-small cell carcinoma, and others using hospital-based NGS (CGP) and large cell carcinoma. A hybrid-capture based NGS assay to a mean coverage depth of 576X was used. Results: Overall, there were 6728 instances of EGFR exon 21 L858R (359) and L858Q (20), exon 18 G719X (73) and exon 20 S768I (30), pm that of 103 unique cases had prior EGFR testing results that were available for review. Of these 103 cases, CGP identified 22 patients (21%) with sensitizing EGFR pm that were not detected by SOC testing, including 9/75 (12%) patients with L858R, 4/7 (57%) patients with L858Q, 8/20 (40%) patients with G719X and 4/7 (57%) patients with S768I pm that were not detected by SOC testing. Our aim is to compare the detection rates of CGP versus SOC testing for well-characterized sensitizing EGFR point mutations (pm) in the 6832 patient cohort. Results: DNA was extracted from 40 microns of FFPE sections from 6832 consecutive cases of lung adenocarcinoma, adenosquamous carcinoma, non-small cell carcinoma, and others using hospital-based NGS (CGP) and large cell carcinoma. A hybrid-capture based NGS assay to a mean coverage depth of 576X was used. Results: Overall, there were 6728 instances of EGFR exon 21 L858R (359) and L858Q (20), exon 18 G719X (73) and exon 20 S768I (30), pm that of 103 unique cases had prior EGFR testing results that were available for review. Of these 103 cases, CGP identified 22 patients (21%) with sensitizing EGFR pm that were not detected by SOC testing, including 9/75 (12%) patients with L858R, 4/7 (57%) patients with L858Q, 8/20 (40%) patients with G719X and 4/7 (57%) patients with S768I pm that were not detected by SOC testing. Conclusion: Hybrid-capture based CGP is an ultra-sensitive assay that even when using low tumor purity clinical-grade specimens, can detect well-known sensitizing EGFR pm with high sensitivity and specificity.

Keywords: comprehensive genomic profiling, EGFR, hybrid-capture

PUB106 DIFFERENT ALK/ROS1 VARIANTS IN PROGNOSIS OF SURGICAL NSCLC PATIENTS

Chao Zhao, Xuefei Li, Chunxiao Su, Shengxiang Ren, Xiaoxia Chen, Caicun Zhou

Shanghai Pulmonary Hospital, Shanghai/China

Background: The roles of different ALK variants in advanced stage non-small cell lung cancer (NSCLC) patients have been reported, however, the roles of different ALK/ROS1 variants in surgical NSCLC patients have not been studied. Methods: EGFR/ALK/ROS1 were detected in 1101 surgery samples in Shanghai pulmonary hospital using ARMS method and multiplex RT–PCR, and ALK/ROS1 fusion positive samples were confirmed by DNA sequencing. The clinicopathologic features and prognosis of the ALK/ROS1 fusion positive patients were analyzed. Results: 78 samples (7%) were ALK fusion positive, and 72 were confirmed by DNA sequencing: 18 (25%) ALK variant1, 15 (20.8%) v2, 31 (43.3%) v3 and 8 (11.1%) other fusion types. 26(2.4%) were ROS1 fusion positive, and all were confirmed: 1 (3.8%) SL exon 4 with ROS1 exon 32 (SL E4:ROS1 E32, R1); 4 (15.4%) SOC4:E2:ROS1 E32 (R2); 13 (50.0%) CD74 E6:ROS1 E34 (R3); 3 (16.7%) SL3CA24 E4:ROS1 E32/34 (R4); 3 (13.8%) LRG11 E16:ROS1 E35 (R5); 4 (15.4%) EKR10:ROS1 E34 (R6). ALK fusion v3 and the other 8 fusion types were all found only in adenocarcinoma (p=0.022). ROS1 fusions were mostly found in female (p=0.049) and never/light smoking (p=0.025) patients. R3 fusion was most likely to be found in female (11 of 13 cases, 84.6%) and never/light smokers (12 of 13 cases, 92.3%). Only part of the patients got DFS data, and they suggested that DFS of ALK v3 and other fusions were longer than v1 and v2 (p=0.025); ROS1 R3 was longer than R2, R4 and R6 (p=0.005). Conclusion: ALK fusion was found 7.1% and ROS1 was 2.4% in surgical NSCLC patients. Different ALK/ROS1 fusions may affect the DFS of these patients.

Keywords: lung cancer, ALK, ROS1

PUB107 CANCER GENOMIC RESOURCES AND NEEDS IN THE LATIN AMERICAN REGION

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Background: One of the priorities of cancer control within the Latin American (LA) region is to reduce avoidable deaths from cancer by improving early detection and personalized treatment. The development of cancer genomics and their integration to cancer care has shown a great improvement in cancer control worldwide. However, all these key advances have been mainly concentrated in high income nations and little is known about the capacities and needs of cancer genomics in the Latin American context. Methods: We collected available online information for all countries in central, South America and Cuba. Data reviewed included: number of cancer research institutions, number of Next Generation Sequencing (NGS) platforms, number of research groups working in cancer genetics, publications on cancer genetics for the last 10 years, educational programs on genomics and related health policies. Results: Map 1. shows the distribution of Educational Programs, research groups and NGS platforms by country. The number below country name correspond to the regional distribution of platform technology. Conclusion: In average, 15 Research groups per country were registered as conducting cancer-genetics related projects. In the last 10 years, 206 publications on cancer genetics including reviews were led by (1st, 2nd or corresponding) authors affiliated to LA institutions (Figure 1) and only 56 publications in the last 2 years included cancer genomic analysis. The number of platforms is lower than other developed regions but it could be considered sufficient to cover the current needs of the regions. However, There is a need of more technical and scientific specialization in this field to increase the base of knowledge of cancer genomics and to have a positive impact in the number of publications.

Keywords: Latin America, Cancer Genomics
Abstracts

PUB108 CONCURRENT NAB-PACLITAXEL/CARBOPlatin COMBINED WITH THORACIC RADIOTherapy IN LOCALLy ADVANCED SQUAMOUS CELL LUNG CANCER (NCT01494415)
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Background: Chemoradiotherapy is the standard treatment for locally advanced squamous cell lung cancer, however, treatment development is urgently needed due to poor prognosis and significant toxicity. Combination therapy of carboplatin and nab-paclitaxel is a useful choice as first-line therapy for patients with advanced non-small cell lung cancer, especially for squamous cell cancer. This prospective phase II study was conducted to explore the efficacy and toxicity of concurrent chemoradiotherapy with nab-paclitaxel, carboplatin and thoracic radiotherapy in unresectable locally advanced squamous cell lung cancer. Methods: Patients with unresectable Stage III squamous cell lung cancer were eligible. Patients received nab-paclitaxel weekly at a dose of 60mg/m², in combination with carboplatin (area under the plasma concentration time curve (AUC) 2) weekly during concurrent chemoradiotherapy. Thoracic radiation was administered at a dose of 66Gy/33 fractions, both three dimensional conformal and intensity modulated radiation therapy were allowed. The consolidation phase chemoradiotherapy consisted of full dose nab-paclitaxel (260 mg/m² on day 1) and carboplatin (AUC 6 on day 1) every 21 days was administered in two cycles after the concurrent chemoradiotherapy. The primary endpoint was objective response rate (ORR). Secondary endpoints included progression-free survival (PFS), overall survival (OS), acute radiation esophagitis and pneumonitis. (Clinical trial registration: NCT01494415). Results: Initially, enrollment of 21 patients was planned; however, the trial was prematurely closed due to slow recruitment. Finally, a total of 8 patients were enrolled between January 2012 and July 2015 from one institute. All patients completed concurrent chemoradiotherapy and 6 patients (75.0%) received consolidation chemoradiotherapy. The objective response rate was 62.5%, with partial remission 5 (62.5%), stable disease 2 (25.0%), progressive disease 1 (12.5%), respectively. After a median follow-up of 11.6 (range, 2.0–29.2) months, 5 patients were dead, 3 were alive. The median progression-free survival and overall survival were 12.1 months and 15.2 months, respectively. According to Common Terminology Criteria for Adverse Events (CTCAE) version 4.0, 6 patients (75.0%) experienced acute radiation esophagitis, 4 (50.0%) were grade 2 (G2), 2 (25.0%) were G3; 4 patients (50%) experienced acute radiation pneumonitis, 3 (37.5%) were G2, 1 (12.5%) were G3. No late radiation-induced esophageal and pulmonary toxicity was observed after 1-year follow-up.

Conclusion: Concurrent nab-paclitaxel, carboplatin and thoracic radiotherapy is showed to be an effective regimen for patients with unresectable locally advanced squamous cell lung cancer. However, further study should exercise caution due to the severe toxicity of radiation tissue injury especially acute radiation esophagitis.

Keywords: concurrent chemoradiotherapy, Squamous cell lung cancer, nab-paclitaxel

PUB109 EFFICACY OF EARLY AUTOLOGous BLOOD-PATCH ADMINISTRATION FOR AIR LEAK AFTER PULMONARY RESECTIONS
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Background: Prolonged air leak is a common complication after pulmonary resections and is the major cause of late hospital discharge. The aim of this study was to determine the efficacy of autologous blood-patch (ABP) administration in patients with air leaks after anatomic pulmonary resections. Methods: Between January 2010 and December 2015, ABP pleurodesis was performed to 44 patients (37 males, 7 females) who underwent anatomic pulmonary resection with the diagnosis of non-small cell lung cancer our clinic. The patients were divided into two groups: patients who received their ABP in postoperative first four days (Group 1) and after postoperative day four (Group 2). Durations of air leaks and chest tube drainage in these two groups were compared retrospectively. Results: The mean age of the patients was 59.68 ± 9.90 years (range, 29 to 74 years). Right upper lobectomy was the most performed resection in 17 (38.6%) patients. The mean duration of chest tube drainage was 9.70 ± 3.65 days (range, 4 to 19 days). Two groups were compared in the means of duration of chest tube drainage and it was significantly shorter in Group 1 (7.23 ± 2.63 days vs 12.18 ± 2.73 days, p<0.0001). There was no difference between groups in terms of the stoppage duration of the air leak after ABP administration. Conclusion: As a result, we concluded that ABP is a safe, simple and effective procedure for the management of air leaks after pulmonary resections. Early administration of ABP in such patients shortens chest tube duration and hospital stay.

Keywords: autologous blood-patch, prolonged air leak, pulmonary resection

PUB110 CLINICAL RESULTS OF AN EPID-BASED IN-VIVO DOSIMETRY FOR LUNG CANCER RADIATION THERAPY
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Background: In-vivo dose verification is a step of quality assurance to ensure that the dose delivered during treatment agrees with the prescribed. This work reports the in-ivivo dosimetry (IVD) results obtained with SOFTDISO (Best Medical Italy). Methods: SOFTDISO was developed by National Institute of Nuclear Physics and Catholic University of Sacred Heart (Rome). The software reconstructs in quasi-real time the dose at isocenter (Diso) from the transit signal acquired by the EPID and the comparison between EPIDs of every fractions. For each beam and fraction, the R ratios between Diiso in 3D-CRT plans for lung targets and the dose (2 Gy/fraction) calculated by the treatment planning system Diso, TPS (Oncentra) were computed. The acceptance criteria was 0.95< R<1.05. The y-analysis (DD<5%; Dd=5mm) between EPIDs to test the beam delivery reproducibility with the Pyc1>90% and ymean<0.5 was performed. Fourteen patients with lung cancer were treated with 6 MV photon beams delivered by an Elekta Synergy Agility. The pass criteria was Dd equal to the mean distance (mm) along x, y, z directions, accepted in the patient set-up reproducibility. The IVD test were performed twice weekly when the CBCT wasn’t acquired. Results: The IVD supplied 682 tests. The tests of tolerance were >13% for R, >35% for Pyc1 and >16% for ymean. For each patient the Rmean value was within the tolerance level. As regards Pyc1 and ymean, 70% and 86% of patients had values within the tolerance, respectively. These values were obtained considering set-up errors and morphological changes (tumor reduction, atelectasis and/or air). Figure 1 shows the results in one patient.

(See Figure next page)
Conclusion: Results of an EPID-based in-vivo dosimetry for lung cancer treatments are in tolerance for the dose at the isocenter (R-value). The γ-analysis suffer from some restrictions due to morphological changes that affect the results. The SOFTDISO real-time analysis allows to daily investigate the dose delivery.

Keywords: quality assurance, EPID, In-vivo dosimetry

PUBL111 DELINEATING MEDIASTINAL LYMPH NODAL CLINICAL TARGET VOLUME: COMPARISON OF TWO ATLASES AND PRACTICAL IMPLICATIONS

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Background: Variations in target volume delineation represent a significant hurdle in conformal radiotherapy. In Non Small Cell Lung Cancer, the delineation of nodal clinical target volume (CTV) has been studied. We compared Chapet recommendations (IJRBP, 2005) with our institutional atlas (“A Guide for Delineation of Lymph Node Clinical Target Volume: Radiation Therapy”, Ausili Cefaro G. et al. 2012) about the definition of the radiologic boundaries of Mountain and Dresler’s thoracic lymph node stations (LNS) on CT. Methods: Chapet’s and our contouring atlas were reviewed. Regional lymph nodes were delineated as separate CTVs using Mountain and Dresler classification (1997). Two different modalities to define LNS localization were compared. Results: Chapet combined stations 1 and 2 on the right (R) and lest (L) side, assuming that they often cover a short vertical distance and that station 2R is “virtual” in some patients. We distinguished these stations and proposed a separate description of the boundaries of stations 1R-1L and 2R-2L. While Chapet indicated left subclavian artery and left common carotid artery as vessels that describe the anterior boundary of the combined 1L-2L, we considered them as posterior part of 1L. This discrepancy may be explained by the different estimation of the upper limit of 1L that in our atlas is more cranial (thoracic inlet) because we considered a longer segment of subclavian and common carotid arteries thus including their posterior course. In our atlas, a plane touching the top of sternal manubrium and a horizontal plane passing through the superior margin of aortic arch are the cranial and caudal boundaries of 3A, respectively. Conversely, Chapet proposed the carina as the 3A inferior limit. Chapet located the origin of the right middle lobe bronchus in the inferior limit of 7, whereas we chose the right pulmonary artery. As station 6 caudal limit, we proposed a horizontal plane passing the auricle of right atrium while for Chapet was the lowest image where the right pulmonary artery is viewed. In our atlas the diaphragm is the caudal limit of station 8, as the gastroesophageal junction was for Chapet. Chapet described better limits for hilar LNS (10-11 R and L) than us. Conclusion: Standardized delineation of nodal areas is important. In our daily experience, our atlas is easy to use and reproducible with clearly recognizable limits. However, the atlas should be adapted to the needs and to the planning techniques (3DCRT, IMRT-VMAT, SBRT) employed in each single institution.

Keywords: CTV, mediastinal lymph nodes, contouring

PUBL12 COMPARISON OF TWO ATLASES TO DELINEATE ORGAN AT RISKS CONTOURING IN LUNG CANCER RADIATION THERAPY

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Background: Dosimetric constraints of thoracic organs at risk (OARs) have been used in institutional and multicentric trials in cooperative groups such as RTOG, EORTC and SWOG. However the anatomic delineation of these structures has not been standardized. Methods: We compared Kong’s recommendations (Kong FM, IJROBP 2011) with our institutional atlas (“Delineating Organs at risk in Radiation Therapy”, Ausili Cefaro G. et al. 2012) for the contouring of thoracic OARs and the definition of their anatomo-radiological boundaries. Results: The following are the main differences and concordances. Esophagus cranio-caudal limits were the same. We defined antero-posterior and latero-lateral boundaries while Kong not. Brachial plexus: in subclavicular neurovascular bundle, many differences were found because of difficult visualization of this structure in CT. Lung: for Kong, lung was the air-inflated parenchyma without proximal bronchial tree, fluid and atelectasis. Our atlas, provided proper cranial, caudal, medial, lateral, anterior e posterior limits. Proximal bronchial tree: we gave the air-inflated parenchyma without proximal bronchial tree, fluid and atelectasis. Our atlas, provided proper cranial, caudal, medial, lateral, anterior and posterior limits. Proximal bronchial tree: we gave the air-inflated parenchyma. Conclusion: Standardized delineation of OARs are crucial for clinical trials and daily practice. In our experience, we clinically are checking our atlas that is easy to use and reproducible with clearly recognizable limits. However, the atlas should be adapted to the needs and to the planning techniques (3DCRT, IMRT-VMAT, SBRT) employed in each single institution.

Keywords: organs at risk, contouring
Abstracts

**PUB13 ORGANS AT RISK CONTOURING IN LUNG CANCER RADIATION THERAPY: AN ANATOMO-RADIOLOGICAL ATLAS**

Maria Taraborrelli, Marianna Nuzzo, Annamaria Vinciguerra, Marianna Trignani, Francesca Perrotti, Clelia Di Carlo, Saide Di Biase, Consuelo Rosa, Domenico Genovesi

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**Background:** The accuracy of organ at risk (OARs) delineation may impact on dosimetric parameters and influence the treatment planning. In thoracic radiation therapy, the normal tissues are often dose limiting. Aim of this study is to provide anatomical boundaries for the correct identification and contouring of OARs in thoracic district. **Methods:** A dedicated thoracic Radiologist, a Neuro-radiologist and three Radiation Oncologists were gathered to generate a 3D radiologic description of the thoracic OARs on axial CT scans. This interdisciplinary team provides anatomical boundaries detectable on planning CT for each thoracic OAR (“Delineating Organs at risk in Radiation Therapy”, Ausili Cefaro G. et al. 2012). **Results:** Three-dimensional descriptions of lung, esophagus, proximal bronchial tree, spinal cord, heart and brachial plexus were performed. A CT atlas was developed with definition of cranial, caudal, anterior, posterior, medial and lateral limit for each OARs (table 1).

<table>
<thead>
<tr>
<th>OARs</th>
<th>Cranial</th>
<th>Caudal</th>
<th>Lateral</th>
<th>Medial</th>
<th>Anterior</th>
<th>Posterior</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>Line through posterior arch of the first rib</td>
<td>Diaphragm</td>
<td>Chest wall</td>
<td>Large mediastinal vessels. Cardiac chambers.</td>
<td>Chest wall</td>
<td>Chest wall</td>
</tr>
<tr>
<td>Heart</td>
<td>Line through inferior edge of left main pulmonary artery</td>
<td>Line through superior edge of the left hepatic lobe</td>
<td>Mediastinal pleura. Lung parenchyma.</td>
<td>/</td>
<td>Adipose tissue of the anterior mediastinum.</td>
<td>Esophagus. Descending aorta.</td>
</tr>
</tbody>
</table>

**Conclusion:** The contouring atlas for thoracic OARs represents a considerable tool in our clinical practice. We believe that the development of interdisciplinary atlas is a formative tool to optimize both 3D-CRT and IMRT-VMAT planning.

**Keywords:** organs at risk, contouring, atlas

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**PUB14 DOSE-RESPONSE RELATIONSHIP FOR SAFETY AND EFFICACY USING STEREOTACTIC BODY RADIATION THERAPY FOR CENTRALLY-LOCATED NON-SMALL CELL LUNG CANCER**

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**Background:** Stereotactic body radiation therapy (SBRT) has become a standard treatment for inoperable peripherally-located early-stage non-small cell lung cancer (NSCLC). However, the role of SBRT for centrally-located lesions remains controversial because of the potentially severe toxicity. This study was to evaluate the dose-response relationship for safety and efficacy using SBRT for centrally-located NSCLC. **Methods:** Eighty patients (56 male and 24 female) with centrally-located NSCLLC treated with Cyberknife were enrolled between 2006 and 2015. The primary endpoint was the toxicity. The second endpoints were overall survival (OS), progression-free survival (PFS), local control rate (LC), and pattern of failures. The median age was 71 years (range, 51-85). All included patients were confirmed by histologically and PET-CT or CT. Thirty-seven patients had T1 cancer, 33 had T2a, 9 had T2b and 1 had T3. All patients didn’t perform surgery due to organs dysfunction (38.8%), elderly (26.2%), refusal (23.7%), compromised with central lesions (7.5%), and low PS score (3.8%). The planning target volume (PTV) was constructed by adding a 5-mm margin to the gross tumor volume (GTV). The PTV dose was prescribed with a median 74% (range, 58%-80%) isodose line, which covered at least 95% of the PTV. The median PTV volume was 52.2 mL (range, 2.8-264.5), the median prescription dose was 56 Gy (range, 48-60) in 6 fractions (range, 3-10), and the median BED10 was 102.6 Gy (range, 81.3-151.2). Forty-one and 39 patients received Xsight and synchrony tracking model. **Results:** Median follow-up was 22.6 months (range, 2-68.2). CTCAE v4.0≥Grade 3 toxicities occurred in one patient, who died from radiation pneumonitis. Moreover, the occurrence of stenosis and occlusion in lobe bronchus was significantly related with D1 (p < 0.05) other than D01, D0.5, D2, D3, and D5 (all p > 0.05). The median OS, 3-year, and 5-year OS were 37.9 months, 51.7%, and 36.8%, respectively. The 3-year and 5-year cancer-specific OS were 63.6% and 52.5%, respectively. The median PFS, 3-year, and 5-year PFS were 26.1 months, 42.5%, and 25%, respectively. The 1-year and 5-year LC rates were 97.1% and 95.6%, respectively. Nine patients (11.3%) and 31 patients (38.8%) had local and regional recurrence as well as distant metastases, respectively. **Conclusion:** SBRT is a safe and efficacious treatment strategy for centrally-located NSCLC. We recommended that the prescription dose and fractionation modality were
given considering potential toxicity except for the patient’s characteristics. And selected patients may require adjuvant chemotherapy in light of the high rate of distant metastasis.

**Keywords:** efficacy, centrally located non-small cell lung cancer, Stereotactic body radiation therapy, Safety

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**PUB115 CLINICAL STATUS OF PD-L1 AND THE EXPRESSION OF PD-1 IN TUMOR-INFILTRATING LYMPHOCYTES (TILS) IN LUNG CANCER**

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**Background:** PD-L1 status in lung cancer may be a predictive biomarker for the use of PD1/PD-L1 inhibitors. Nonetheless, it is still unclear which immunohistochemistry platform for PD-L1 assessment should be implemented for optimal prognostic/predictive information. We investigated whether the PD-L1 status in early-stage lung cancer is associated with specific clinical features or survival, as well as the PD1 expression in TILS.

**Methods:** IHC was performed on FFPE surgical tumors, arrayed on tissue microarrays with duplicate cores. PD-L1 status was assessed with two Abs: Ventana (SP124) (PD-L1V) and Cell Signaling (E1L3N) (PD-L1CS). PD1 expression in TILs was determined with the Ab Ventana (NAT105). All patients (n=482) had early stage T1/T2/N0 and underwent curative surgery between 1987 and 2002. PD-L1 membranous staining was scored as positive if >5% of tumor cells. PD1 was considered as positive if >10% in TILs.

**Results:** 12% 4% 37%/55%/7%, p-stage IA/IB 52%/58%. A table shows the association depending on the presence of ER-beta in the tumor tissue; the treatment response of lung adenocarcinoma patients affecting by lung cancer than smoking men. There are two tipes of estrogen receptors (ER) - alpha and beta. ER-beta expression is significantly higher in lung cancer than ER-alpha expression. **Methods:** The objectives of this study were to establish the treatment response of lung adenocarcinoma patients depending on the presence of ER-beta in the tumor tissue; the treatment response and survival differences between the sexes depending on the ER-beta status, and finally whether the ER-beta status may be a prognostic factor in these patients. The study included 200 patients with diagnosis of lung adenocarcinoma (diagnosis were established during 2010 according to 5-year survival rate).

**Conclusion:** Neither was statistically significant difference registered in the time passing till the onset of the disease progression in the overall examined females, in whom it was 16.5 and 9.5 months with ER-beta+ and ER-beta - tumor status respectively making statistically significant difference (p=0.04). The analysis of the cumulative survival depending on patients' sex and receptor status (males ER-beta-, males ER-beta+, females ER-beta-, females ER-beta+) has revealed that ER-beta+ females had a significantly longer survival than other three subgroups. **Conclusion:** The obtained results suggest a conclusion that the hormonal receptor status is one of many factors in lung cancer carcinogenesis and may be establish as a prognostic factor in lung cancer, as well as a potential factor in multimodal (hormonal anti-estrogen) treatment of malignancy.

**Keywords:** SCLC, Neurointellectual impairment, PCI, Hypofractionation

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**PUB116 SHORT COURSE PROPHYLACTIC CRANIAL IRRADIATION FOR SMALL CELL LUNG CANCER - ANALYSIS OF EFFICACY AND IMPACT ON NEURO-INTELLECTUAL FUNCTION**

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**Background:** Prophylactic cranial irradiation (PCI) plays a crucial role in prevention of brain metastasis for patients having small cell lung cancer (SCLC) – it be limited stage (LS) or the extensive one (ES). Contrary to conventional 30 Gy/10 fractions, this study aims to find the safety and efficacy of short course PCI with 20 Gy/5 fractions and to analyze its impact on neurointellectual impairment (NIP) with special focus on any possible influence of age and medical co-morbidities. **Methods:** This is an on-going multicentric trial initiated in February 2012 where both LS and ES-SCLC patients who responded to initial therapy are offered PCI for a dose of 20 Gy in 5 fractions with CT-based planning. All patients received Platinum + Etoposide for 6 cycles. LS-SCLC patients received, in addition, concomitant thoracic irradiation after 2 cycles of chemotherapy. All relevant medical co-morbidities (Diabetes, Hyperlipidemia, previous history of CVA) are carefully recorded. Neuropsychological screening measure of immediate and delayed verbal memory by using Hopkins Verbal Learning Test - Revised (HVLT-R), assessment of cognitive function using Mini-Mental Status Examination (MMSE) and Instrumental Activities of Daily Living (IADL) questionnaires are applied before initiation of PCI and on follow up at 3 monthly interval.

Results: Results of first 42 patients receiving PCI (LS-SCLC= 28, ES-SCLC = 14) with minimum follow up of 18 months is presented. Brain metastasis was in none. Median survival was 9 months for ES and 14.5 months for LS-SCLC. 2/18 LS-SCLC and 18/28 LS-SCLC lived one year. Corresponding data for 18 months is 0/14 and 5/28 respectively. MMSE deterioration was noted in 18/21 patients. Subanalysis of 18/37/11 (of the age group of 55 - 65 years (N=24) and remaining 15 were above 65 (N = 18); p < 0.0001. Interestingly all 3 of these below 65 years patients and 13/15 of above 65 years patients were having long-standing hyperlipidemia and nearly half of them were Diabetic also. NSCLC declined in immediate recall (16/42) was in 14/18 patients having MMSE deterioration. Subanalysis of NIP revealed its presence among 14/20 patients having medical co-morbidities (Hyperlipidemia, Diabetes etc) and in only 2/22 without any (p < 0.0001).

**Conclusion:** 20Gy/5 fractions is an effective patient-compliant PCI protocol for both LS and ES – SCLC only for well-selected patients aged below 65 years without medical comorbidities, specially those which have established role in causing cerebral microinfarcts.

**Keywords:** SCLC, Neurointellectual impairment, PCI, Hypofractionation

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**PUB117 BETA ESTROGEN RECEPTOR AS POTENTIAL PROGNOSTIC FACTOR IN LUNG ADENOCARCINOMA**

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**Background:** The greater lung cancer incidence in the female population has been primarily correlated to the increasingly present smoking habit among females all over the world. The hormonal estrogen status has been reported as another possible factor contributing to the increasing incidence of lung cancer in females, due to the fact that still a lower percentage of smoking women is affected by lung cancer than smoking men. There are two tipes of estrogen receptors (ER) - alpha and beta. ER-beta expression is significantly higher in lung cancer than ER-alpha expression. **Methods:** The objectives of this study were to establish the treatment response of lung adenocarcinoma patients depending on the presence of ER-beta in the tumor tissue; the treatment response and survival differences between the sexes depending on the ER-beta status, and finally whether the ER-beta status may be a prognostic factor in these patients. The study included 200 patients with diagnosis of lung adenocarcinoma (diagnosis were established during 2010 according to 5-year survival rate).

**Results:** Neither was statistically significant difference registered in the time passing till the onset of the disease progression in the overall examined females, in whom it was 16.5 and 9.5 months with ER-beta+ and ER-beta - tumor status respectively making statistically significant difference (p=0.04). The analysis of the cumulative survival depending on patients' sex and receptor status (males ER-beta-, males ER-beta+, females ER-beta-, females ER-beta+) has revealed that ER-beta+ females had a significantly longer survival than other three subgroups. **Conclusion:** The obtained results suggest a conclusion that the hormonal receptor status is one of many factors in lung cancer carcinogenesis and may be establish as a prognostic factor in lung cancer, as well as a potential factor in multimodal (hormonal anti-estrogen) treatment of malignancy.

**Keywords:** survival rate, lung adenocarcinoma, prognostic factor, beta estrogen receptor

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**PUB118 PRE-CHEMOTHERAPY EGFR MUTATION STATUS & OUTCOMES WITH SECOND LINE GEFITINIB IN ADVANCED ADENOCARCINOMA LUNG**


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Abstracts

Background: This study has been planned to evaluate the differential effect of EGFR mutation status done prior to first line Pemetrexed-Carboplatin chemotheraphy on PFS and OS in advanced stage adenocarcinoma lung NETs treated with Gefitinib as second line agent. Methods: This was a post hoc analysis of a phase III study comparing Pemetrexed-Carboplatin vs Gefitinib in first line setting. Patient who had exon 19 or 21 mutation, subsequent had progressed on Pemetrexed-Carboplatin in first line setting and received Gefitinib in second line were selected for this analysis. Patients were treated with Gefitinib 250 mg daily. Axial imaging for response assessment was done every 2 months till progression. If patients had partial response or stable disease, they were continued on Gefitinib until progression or unacceptable toxicity. Kaplan-Meier method was used for survival estimates, log rank test was used for comparison. A p value of 0.05 was considered as significant.

Results: 112 patients received Gefitinib as second line therapy. 36 patients (32.1%) had exon 21 while 76 patients (67.9%) had exon 19 mutation (p=0.016). Median progression free survival and OS for exon 19 was 8.1 months [95% CI 6.9-9.6 months] vs 5.8 months [95% CI 3.8-7.7] months (p=0.163) in exon 21 mutated patients. The median overall survival was 17.8[95% CI 13.1-22.7] months in exon 19 mutated patients against 9.6[95 % CI 6.0-13.3] months in exon 21 mutated patients (p=0.001). Conclusion: Pre-chemotherapy EGFR mutation status predicts for response and OS to Gefitinib in second line setting in patients with advanced Adenocarcinoma lung.

Keywords: EGFR mutation, Second Line, Gefitinib, Adenocarcinoma

PUB19 LANREOTIDE IN PATIENTS WITH LUNG NEUROENDOCRINE TUMORS: THE RANDOMIZED DOUBLE-BLIND PLACEBO-CONTROLLED INTERNATIONAL PHASE 3 SPINET STUDY
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Background: Surgery remains the mainstay for localized lung neuroendocrine tumors (NETs), while other approved treatment options for advanced lung NETs are currently limited. The large phase 3 CLARINET study demonstrated antitumor efficacy of the somatostatin analog (SSA) lanreotide autogel/depot (LAN) 120 mg vs placebo (PBO) for metastatic gastroenteropancreatic (GEP)-NETs of grade 1 or 2 (Ki-67 ≤10%). CLARINET did not evaluate LAN in advanced lung NETs, and prospective studies of SSA therapies for these NET subtypes are currently lacking. The objective of the SPINET study is to evaluate the safety and antitumor efficacy of LAN 120 mg in patients with advanced lung NETs.

Methods: SPINET is a large multinational, multicenter, randomized, double-blind, PBO-controlled phase 3 study (NCT02683941; EudraCT: 2015-004992-62). Main inclusion criteria are adult patients with well-differentiated typical or atypical, metastatic and/or unresectable lung NETs. Positive somatostatin-receptor imaging, typical or atypical, metastatic and/or unresectable lung NETs, and prospective studies of SSA therapies for these NET subtypes are currently limited. The large phase 3 CLARINET study demonstrated antitumor efficacy of the somatostatin analog (SSA) lanreotide autogel/depot (LAN) 120 mg vs placebo (PBO) for metastatic gastroenteropancreatic (GEP)-NETs of grade 1 or 2 (Ki-67 ≤10%). CLARINET did not evaluate LAN in advanced lung NETs, and prospective studies of SSA therapies for these NET subtypes are currently lacking. The objective of the SPINET study is to evaluate the safety and antitumor efficacy of LAN 120 mg in patients with advanced lung NETs.

Methods: This was a post hoc analysis of a phase III study comparing Pemetrexed-Carboplatin vs Gefitinib in first line setting. Patient who had exon 19 or 21 mutation, subsequent had progressed on Pemetrexed-Carboplatin in first line setting and received Gefitinib in second line were selected for this analysis. Patients were treated with Gefitinib 250 mg daily. Axial imaging for response assessment was done every 2 months till progression. If patients had partial response or stable disease, they were continued on Gefitinib until progression or unacceptable toxicity. Kaplan-Meier method was used for survival estimates, log rank test was used for comparison. A p value of 0.05 was considered as significant.

Results: 112 patients received Gefitinib as second line therapy. 36 patients (32.1%) had exon 21 while 76 patients (67.9%) had exon 19 mutation (p=0.016). Median progression free survival and OS for exon 19 was 8.1 months [95% CI 6.9-9.6 months] vs 5.8 months [95% CI 3.8-7.7] months (p=0.163) in exon 21 mutated patients. The median overall survival was 17.8[95% CI 13.1-22.7] months in exon 19 mutated patients against 9.6[95 % CI 6.0-13.3] months in exon 21 mutated patients (p=0.001). Conclusion: Pre-chemotherapy EGFR mutation status predicts for response and OS to Gefitinib in second line setting in patients with advanced Adenocarcinoma lung.

Keywords: EGFR mutation, Second Line, Gefitinib, Adenocarcinoma

PUB120 RESEARCH ON THE ROLES AND MOLECULAR MECHANISMS OF RAF1/P70S6K SIGNALING PATHWAY IN NON-SMALL CELL LUNG CANCER
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Background: Lung cancer is the first malignant and morbidity tumor worldwide, and non-small cell lung cancer (NSCLC) is the main type. Majority of patients with lung cancer died because of metastasis and recurrence of tumors. In order to prolong patients’ survival rate, early diagnosis and development of more effective drug treatment become the main research direction to clinical doctors and scientists. However, previous research of our team found that expression of p70S6K protein was significantly suppressed after silencing Raf1 gene expression, and overexpression of p70S6K had worse survival prognosis in patients with NSCLC. But, whether p70S6K is regulated after silencing of Raf1 is still not clear. Therefore, our aim of this research is to explore the cross talk between Raf1 and p70S6K in NSCLC.

Methods: The construct of the lentivirus RNA vector targeting Raf1 and p70S6K were verified by sequencing. Co-infection systems were composed with shRaf1 and p70S6K overexpression lentiviral vectors. Western blot was used to tested p70S6K and Raf1 protein expression level of each cell line. Status of proliferation, apoptosis and cycle were observed in vitro. Ability of tumorigenesis of NSCLC cells were assessed using nude mouse models in vivo. Results: We obtained the stable cell clones of silenced Raf1 gene expression, overexpression of p70S6K and co-expression of Raf1 and p70S6K. In vitro, the function of cell proliferation, apoptosis and cycle of co-infected groups were located between shRaf1 groups and OE-p70S6K groups. The weight and volume of transplanted tumors of co-infected groups were obviously higher than shRaf1 groups and lower than OE-p70S6K groups. Results of Ki-67 and TUNEL examination were consistent with experiment in vitro and in vivo. The figures below only show the results in vivo.

Keywords: Lung neuroendocrine tumors, Lanreotide, Progression-free survival
Conclusion: Targeted silence Raf1 expression joint p70S6K overexpression had antagonism effect to the biological behavior of NSCLC. Raf1 might affect the biological behavior of NSCLC according to p70S6K.

Keywords: Raf1, non-small cell lung cancer, p70S6K, co-infected

PUB122 ASSESSMENT OF PROGNOSTIC SCORES IN BRAIN METASTASES FROM LUNG ADENOCARCINOMA WITH STATUS OF EGFR MUTATIONS

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Background: Our purpose was to analyze the prognostic factor and evaluate the value of four prognostic scores including RPA, DS-GPA, BS-BM, GGS for the EGFR mutant BM patients from lung adenocarcinoma treated with EGFR-TKI. Methods: The data of NSCLC were retrospectively reviewed from August 2010 to June 2015 in medical database of Shanxi Provincial Cancer Hospital. Patients with BM from lung adenocarcinoma indentified with EGFR mutations received treatment of EGFR-TKI or combination of EGFR-TKI plus WBRT were included. Potential prognostic factors were examined in univariable and multivariable analyses. To compare the predictive values of each scoring system, the C-index of each prognostic score were calculated. Results: A total of 1063 BM patients with lung adenocarcinoma identified with status of EGFR mutations between August 2010 and June 2015 from lung cancer medical database was reviewed. Among them, 104 patients who diagnosed with BM confirmed with status of EGFR mutations in primary tumors. They received treatment of EGFR-TKI or EGFR-TKI plus WBRT to BM. The median survival was 15.83 months (95% CI 14.30–17.36). The 1 year survival rate was 60.3%. The potential predictive factors in multivariable analysis were included KPS (70 vs. 70–80 vs. 90–100), and number of brain metastatic lesions. The potential predictive factors in multivariable analysis, the following were significantly associated with higher radiotherapy RRs: EGFR mutations (OR = 4.262, 95% CI = 1.105–16.435, P = 0.035) and KPS at BM (OR = 8.344, 95% CI = 6.688–41.252, P = 0.009). At the end of the 6-month follow-up, there were 63 patients still alive. The median survival time was 12 months (95% C.I. 9.535–14.65). By the log-rank test, the following were associated with a much longer IPFS: EGFR mutation (P = 0.007), KPS at BM (P < 0.001), and control of primary tumor (P = 0.008). Multivariate analysis further revealed that EGFR mutation and KPS scores at BM were independent effectors (Table 3, Figure 1). The univariate analysis revealed that being female (P = 0.056), control of primary tumor (P = 0.002), and higher KPS scores (P < 0.001) were associated with longer OS. Consistently, by the multivariate analysis, the independent prognostic factors were KPS (P < 0.001), and control of primary tumor (P = 0.031). Conclusion: Our results suggest that EGFR mutations in BM from lung adenocarcinoma treated with longer treatment response and a longer IPFS after WBRT, relative to patients without EGFR mutations. However, an influence on OS was not observed.

Keywords: whole brain radiotherapy (WBRT); brain metastases (BM); lung adenocarcinoma (LA)

PUB123 CORRELATION BETWEEN STATUS OF EPIDERMAL GROWTH FACTOR RECEPTOR MUTATION AND DISTANT METASTASES OF NON-SMALL-CELL LUNG CANCER

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Background: As the important biological marker, EGFR mutation may involve a different biological subtype which has a different clinical profile and path of spread. So our purpose was to explore the correlations between status of EGFR mutations and distant metastases. Methods: A total of 1391 patients with non-small cell lung cancer indentified with status of EGFR mutations from August 2010 to May 2015 at Shanxi Cancer Hospital were enrolled. The associations among EGFR mutations, clinical factors, and distant metastases at initial diagnosis were evaluated. The data of distant metastases of the brain, bone, liver, adrenal gland, and other sites were verified using imaging. The chi-square or Fisher exact test was used to compare the proportion between two groups of patients with and without EGFR mutations among different demographic characteristics. The univariable and multivariable analysis of the correlation between different metastatic sites and clinical characteristics was performed using a logistic regression model. Results: Patients harboring EGFR mutation were more likely to be female (P = 0.001) with no smoking history (P = 0.001), adenocarcinoma (P = 0.001), higher ECOG performance scores (P = 0.049), brain metastases (P = 0.048), lung metastases (P = 0.002), and bone metastases (P = 0.002). The status of EGFR mutation achieved statistical difference both in univariate analysis (P < 0.001), and in multivariate analysis (P < 0.001). The ECOG performance status (P = 0.001), smoking (P = 0.031), pathology (P = 0.001), T stages (P = 0.001) and N stages (P = 0.001) also had a statistically significant correlation with distant metastases. Associations between EGFR mutation status and distant metastases were found in brain (P = 0.001) and lung metastases (P = 0.001) in multivariable analysis, but they were not found with other types of distant metastases. T stages were closely correlated with lung metastases (P < 0.001). The pathologic type of non-squamous cell carcinoma associated with higher brain (P = 0.029), and adrenal gland metastases (P = 0.033) than squamous cell carcinoma. N involvement only showed statistically significant differences for metastasis of the bone (P = 0.029), lung (P = 0.001), brain (P = 0.001), liver (P = 0.005), and adrenal gland (P = 0.005) and other sites (P = 0.001). The results in EGFR subtype analysis showed 19del mutations was associated with total metastases (OR: 1.487, 95% CI: 1.077–2.054, P = 0.016) brain (OR: 1.852, 95% CI: 1.217–2.832, P = 0.004), and lung metastases (OR: 1.726, 95% CI: 1.68–2.55, P = 0.006). The exon 21 point mutations associated with total (OR: 1.398, 95% CI: 1.005–1.945, P = 0.047) and liver metastases (OR: 1.821, 95% CI: 1.052–3.151, P = 0.032). Conclusion: The EGFR mutations in NSCLC are independently correlated with distant metastases. Subgroup analyses showed that patients with 19del mutations probably developed distant metastases more readily than those with exon 21 point mutations.

Keywords: Non-small-cell lung cancer; EGFR mutation; distant metastases
Abstracts

PUB124 THE DIAGNOSTIC VALUE OF PET-CT IN BENIGN LUNG DISEASES
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Background: The sensitivity and specificity of positron emission tomography (PET) in focal lung lesions are approximately 85-90% and 50-100%, respectively. There are many diseases showing high metabolic activity especially although they are not malignant and causing false positivity. In this study we evaluated the results of PET of the patients underwent resection with malignant prediagnosis according to fluorodeoxyglucose (FDG) uptake value but diagnosed as “benignant” pathologically. Methods: The results of 106 (12.3%) patients among 862 patients underwent surgery with prediagnosis of malignant lung according to the PET-CT results but diagnosed as benignant pathologically between January 2012 and December 2015, were analyzed. The diagnosis, standardized uptake values (SUV), operation type and demographic properties of patients were investigated retrospectively. Results: All patients including 89 (54.5%) males and 164 (45.5%) females were 55.5 ± 11.9 years (range, 26 to 79 years). The means of diameter and SUVmax of the lesions were 2 ± 2.14 cm (range, 0.5 to 13 cm) and 3.55 ± 4.35 (range, 0 to 22.2), respectively. Pathology results were analyzed in five different groups: granulomatous diseases 31 (29.3%), hamartomas 19 (17.9%), interstitial lung disease 18 (17%), reactive lymph node 12 (11.3%), others 26 (24.5%). The SUVmax of the hamartomas was significantly lower than the other groups (p<0.001). Conclusion: The false positivity of PET must be keep in mind when using for the diagnosis and treatment of lung cancer. Especially in case of granulomatous disease suspicion all available preoperative diagnostic procedures must be performed and in operations where necessary this suspicion should not be ignored.

Keywords: benign lung disease, Positron emission tomography, Operation

PUB125 CLINICAL OBSERVATION OF NIMOTUZUMAB COMBINED WITH CHEMOTHERAPY AS FIRST LINE THERAPY FOR ADVANCED LUNG QUADEM CELL CARCINOMA
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Background: We found nimotuzumab combined with chemotherapy showed good efficacy in patients with squamous cell lung cancer. Now we try to evaluate efficacy and safety of nimotuzumab combined with chemotherapy as first line therapy for advanced lung squamous cell carcinoma. Methods: A retrospective analysis of clinical data was conducted in patients with advanced lung squamous cell carcinoma, who were treated by nimotuzumab during February 2012 to March 2016 in Department of Respiratory Medicine, Peking Union Medical College Hospital. All patients signed the informed consents, and consented to offer clinical information. Results: 14 patients were enrolled in this study, including 13 male and 1 female patients. Median Age is 69 (52-70) year old. Two patients were of stage IIIB lung cancer, 12 patients of stage IV lung cancer. Results: The mean age of the patients was 57.1%, and 60(6.6%) males and 46 (43.4%) females was 55.5 ± 11.9 years (range, 26 to 79 years). The means of diameter and SUVmax of the lesions were 2 ± 2.14 cm (range, 0.5 to 13 cm) and 3.55 ± 4.35 (range, 0 to 22.2), respectively. Pathology results were analyzed in five different groups: granulomatous diseases 31 (29.3%), hamartomas 19 (17.9%), interstitial lung disease 18 (17%), reactive lymph node 12 (11.3%), others 26 (24.5%). Conclusion: The false positivity of PET must be keep in mind when using for the diagnosis and treatment of lung cancer. Especially in case of granulomatous disease suspicion all available preoperative diagnostic procedures must be performed and in operations where necessary this suspicion should not be ignored.

Keywords: nimotuzumab, chemotherapy, Lung Squamous cell carcinoma

PUB126 THE RETROSPECTIVE ANALYSIS OF ASYMPTOMATIC LUNG CANCER PATIENTS DIAGNOSED INCIDENTALLY
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Background: Lung cancer is the leading cancer type causing death among the world. The patients loose the chance of curative treatment because the disease often entails no symptoms especially in its early stage. In this study we evaluated the lung cancer patients with lesion detected on chest X-ray performed for different reasons, without any respiratory symptom and any malignancy history. Methods: The results of 472 patients underwent surgery for lung cancer between January 2010 and December 2015 analyzed retrospectively. The patients with symptoms cough, spustum, chest pain, dispnea, weight loss or paraneoplastic syndrome findings that can be caused by lung cancer and the patients with malignancy history were excluded. The patients diagnosed as lung cancer incidentally and underwent resection were evaluated. Results: The mean age of the patients, including 110 (83%) males and 22 (17%) females, was 61.12 ± 8.7 years (range, 81 to 38 years) Among these 472 patients 132 (27.9%) were diagnosed as lung cancer incidentally and underwent surgery. Forty-six (35%) patients during surveillance, 44 (33%) patients during controls for other chronic diseases (ischemic heart disease, diabetes mellitus, thyroid disease, etc), 17 (13%) patients during admission to emergency service after trauma, 12 (9%) patients during the evaluation for flu, 7 (6%) patients during the preoperative evaluation for any surgery and 6 (4%) patients during the follow-up for nonspecific complaints were detected incidentally. Anatomic resection to 108 (82%) patients and wedge resection to 24 (18%) patients were performed. The histopathological examination were reported as adenocarcinoma in 77 (58%) patients, squamous cell carcinoma in 39 (29%) patients, neuroendocrine carcinoma in 8 (6%) patients, indifferrant tumor in 4 (3%) patients, small cell carcinoma in 2 (2%) patients and carcinoid tumor in 2 (2%) patients. Conclusion: As a result of this study we realized that, approximately one third of the patients who underwent resection for lung cancer included the patients diagnosed incidentally. We recommend the careful evaluation of radiological examinations which were performed for any reason in terms of any possible lung malignancy.

Keywords: lung cancer incidentally, Operation

PUB127 ROLE OF MICRORNAS AND PROTEOSTASIS SYSTEM IN DIESEL EXHAUST PARTICLE INDUCED LUNG TOXICITY
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Background: Diesel exhaust particle (DEP), is an important ingredient of ambient air, emitting from vehicle exhaust emissions in urban areas considered as pulmonary carcinogen. Animal studies have shown that long-term exposure of DEP induces tumor formation in lungs. Small regulatory RNA molecules known as microRNAs are post-transcriptional gene regulators, which controls the protein synthesis in sequence specific manner. Ubiquilin (UBQLN), a member of ubiquitin-like protein family which are first discovered for their roles in maintaining proteostasis of cells. However, recent studies have shown that UBQLNs also regulate carcinogenesis of lungs. In present study, effects have been made to study the effect of DEP on lung cells and study the role of miRNAs and UBQLNs in DEP induced lung toxicity. Methods: DEP obtained from National Institute of Standards and Technology, Standard Reference material 2975, Gaithersburg, MD was suspended in sterile Milli-Q water followed by sonication at 100 mega hertz. Size distribution and zeta potential of DEP were determined using dynamic light scattering (DLS) and phase analysis light scattering. DEP is further characterized by scanning SEM & Transmission Electron Microscopy (TEM). Internalization of DEP in lung cells was confirmed by TEM. MiRNA profiling of DEP exposed cells was carried out using TDLA arrays of Thermo Scientific as described in our earlier studies. Results: Analyssis of DLS results have shown size of DEP particles between 217 to 225 nm, however TEM imaging have confirmed that size of DEP particles are below 50nm. Exposure of DEP to A549, a lung carcinoma have significantly up-regulated the mRNA and protein levels of UBQLN and down-regulated expression of miR-155, which regulates the expression of UBQLN. Moreover, TEM imaging have shown that over-expression of UBQLN induces accumulation of DEP particles in vacuole like structure in A543 cells. Conclusion: Exposure of nanoparticle sized DEPs up-regulated UBQLN levels in A543 cells and increased expression of UBQLNs induces accumulation of DEP particles in vacuole like structure in A549 cells.

Keywords: Diesel exhaust particle (DEP), Ubiquilin, A543 cells, Mir-155

PUB128 LUNG CANCER INCIDENCE TRENDS IN BELARUS, 1991-2014
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Background: Lung cancer is the most commonly diagnosed cancer among men
and the most frequent cause of cancer mortality in Belarus while the prevalence of smoking remains unacceptably high. The purpose of this research was to investigate trends in lung cancer incidence rates in Belarus. Methods: Data on cases of lung cancer (ICD-10 C34) diagnosed during 24-year period (1991-2014) were obtained from National Cancer Registry. Age-standardized rates (ASRs, World) and cumulative risk were computed for lung cancer overall and by gender. Annual percent change (APC) was calculated by linear regression to characterize trends in lung cancer incidence rates over time for the overall population, by gender, by age group with or without adjustment. Results: During 1991-2014, a total of 103308 lung cancer cases were reported. More incident cases of lung cancer were reported in males (90988) than females (12320). During this period, the average ASRs for lung cancer were 28.66 per 100,000 population and much greater among males (64.24) than females (5.12). The average ASRs were highest among those aged 70-74 years in males (468.2 per 100,000) and 75-79 years in females (45.9 per 100,000). ASRs for males peaked in 1996 (76.1 per 100,000), for females - in 2014 (6.01 per 100,000). From 1991 through 2014, lung cancer incidence rates slightly declined with an APC of -0.52% (95% CI -0.32, -0.63). This decline was pronounced for urban population (APC -1.33%, 95% CI -1.22, -0.84%) while for rural population increase was observed with an APC of 2.36% (CI 2.01, 2.75%)). Among men, lung cancer incidence decreased with APC -0.63% (95% CI -0.83, -0.43), with more expressed tendency in urban population. However, for women incidence rates increased (APC 3.67%, 95% CI 1.05, 1.19). Mean cumulative risk was 12.27% (95% CI 12.09, 12.44) and for men and 1.21% (95% CI 1.17, 1.23) for women. When age subgroups were examined, declines were observed among aged <70 with highest APC in group 50-59 years (-1.66%, CI 1.9, -1.01). In elderly population rates were stable (70-79 years) of increased (>80 years). Among female significant upward trend was observed for middle age group (50-59 years) and for women aged 80 with highest APC 1.84% (95% CI 0.95, 2.74) in age group 60-69 years. Conclusion: Lung cancer mortality trends in males are on a downwards path, while incidence in female may continue to rise, points to an urgent need for prevention strategies among women.

Keywords: Epidemiology, incidence, lung cancer

PUB129 OPTIMAL FREQUENCY OF TUMOUR RESPONSE EVALUATION DURING PALLIATIVE CHEMOTHERAPY IN THE MANAGEMENT OF PATIENTS WITH ADVANCED THORACIC CANCERS
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Background: Tumour response evaluation (TRE) while on palliative chemotherapy for advanced thoracic malignancies is used to assess treatment efficacy. Response Evaluation Criteria In Solid Tumours guides clinical trials, where progression free survival is an endpoint. The frequency of TRE outside of trials is often pragmatic. This study assessed the impact of a change in routine practice from TRE every 2-4 cycles (2C-TRE) to every 3-4 cycles (3C-TRE) on patient care. Methods: The change routine practice was decided on prospectively. Data was collected retrospectively on 2C-TRE between 1 January 2014 and 31 December 2014 and 3C-TRE between 1 March 2015 to 20 January 2016. Results: 433 patient treatment regimens were reviewed, including 220 in 2C-TRE cohort (61% in the 1st line setting) and 213 in the 3C-TRE cohort (71% in the 1st line setting). All patients had advanced stage disease; 56% had non-squamous and 17% had squamous non-small cell lung cancer, 19% had small cell lung cancer, and 8% had mesothelioma. We performed 509 scans/year in the 2C-TRE cohort (2.53 scans/patient; 95% CI: 2.28 - 2.83) and 449 scans/year in the 3C-TRE cohort (2.44 scans/patient; 95% CI: 2.20 - 2.75), inclusive of unscheduled scans. Although there was no difference in the proportion of scans when comparing the 2C-TRE and 3C-TRE cohorts (P = 0.6), there was a significant increase in unscheduled scans from 19% in the 2C-TRE cohort to 26% in the 3C-TRE cohort (P = 0.008). This did not impact on the number of chemotherapy cycles delivered, with 3.6 cycles/patient in the 2C-TRE cohort (95% CI: 3.2 - 4.1) compared with 4.0 cycles/patient in the 3C-TRE cohort (95% CI: 3.6 - 4.6, P = 0.2). Conclusion: The change in practice from 2C-TRE to 3C-TRE during palliative chemotherapy would save us around 60 scans/year, even allowing for 21 unscheduled scans/year. In a hospital that has the capacity to accommodate unscheduled scans, 3C-TRE is a reasonable approach, and would save on resources. However, overall both 2C-TRE and 3C-TRE make no difference to the delivery of chemotherapy both inside and outside of clinical trials.

Keywords: Tumour response evaluation, palliative chemotherapy, advanced thoracic malignancies, optimal frequency

PUB130 THYMIC MALIGNANCIES. A SINGLE INSTITUTION SERIES FROM 2006-2016
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Background: Thymomas and thymic carcinoma are rare malignancies, despite being amongst the most common tumors of the anterior mediastinum. The incidence in the United States (US) is 0.13 per 100,000 habitants per year. Patients with thymoma can be asymptomatic during the diagnosis in 30% to 50% of the cases. The optimal treatment is complete resection. There are two types classification for Thymoma: Masaoka-Koga’s Classification, which assess the grade of invasion, and World Health Organization (WHO) that organize the histologic subtypes. Little information regarding thymic malignancies is available in Latin America. Methods: Retrospective service database review of patients with thymoma treated at Hospital São Lucas between 2006-2016. Inclusion criteria were age 18 or older with histologically confirmed thymoma. Thymomas were classified according to WHO criteria and staging to Masaoka. Results: In eligible patients there were 80% males and 20% females. The mean age was 62 years and 40% were over 65 years. A complete R0 resection was achieved in all cases. No in hospital mortality or morbidity was verified. Conventional open approach was used in 90% and minimally invasive (VATS) in 10%. WHO AB type was the most common with 40% patients, followed by 30% A type, 20% B1 and 10% B2. Masaoka-Koga classification: 70% Type 1, 20% IA and 10% II. The body mass index was normal in half of patients. Myasthenia Gravis was present in 30% and all achieved at least partial response. CKA/E1/3 markers were positive in 60%. Conclusion: Thymoma was most frequent in middle age men. Complete resection was achieved in all cases; predominately Masaoka I stage and WHO AB and type. CKA/E1/3 markers were positive in most cases. Multicenter studies in Latin America should be performed for better understanding of this rare disease.

Keywords: Thymoma, mediastinal tumor
Abstracts

PATIENTS’ PROGNOSIS AT SHANGHAI CHEST HOSPITAL: 2004-2014

PUB132 HEALTH-RELATED QUALITY OF LIFE QUESTIONNAIRES IN LUNG CANCER PATIENTS ATTENDING A TERTIARY CARE HOSPITAL
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Background: Lung cancer is usually diagnosed at an advanced stage and survival has not improved in spite of several therapeutic advancements. Since most patients depend on palliative care, it is imperative to evaluate and maintain a satisfactory quality of life in them. Several questionnaires, mostly in western languages, have been used for this purpose. However, Indian data on this aspect is sparse. Methods: A 26-item WHO-Quality of Life questionnaire in local language was used to assess the quality of life in lung cancer patients attending a tertiary care hospital. The questionnaire comprises four domains—Physical, Psychological, Social and Environmental. Results: A total of 76 patients were evaluated. 66 (86.8%) were males, had a mean age of 55.36 years; presented with cough (82.9%), dyspnoea (72.4%), chest pain (65.8%), and haemoptysis (43.4%). Eight patients (10.5%) had superior venacaval obstruction. The mean duration of symptoms was 5.9 months. 89.5% had Non-Small Cell Cancer (NSCLC). The mean pack-years was 23.7. Most patients had Karnofsky Performance Score (KPS) of 70 (52.6%). There was no significant correlation of any quality of life domain with age, sex, duration of symptoms, extent of smoking, cough, dyspnoea, chest pain, haemoptysis or haemoglobin. The environmental domain correlated significantly with the serum albumin (p<0.016). The physical domain scores of patients with KPS of 80% correlated significantly with those having KPS of 70% and 60% (p<0.001 and p<0.003 respectively). The psychological domain scores of patients with KPS 80% correlated significantly with those having KPS 70% (p<0.005). Conclusion: Quality of life in lung cancer is not affected by age, sex, presence of symptoms and their duration or extent of smoking. Karnofsky Performance Scale is a useful surrogate marker of quality of life in these patients.

Keywords: health, quality of life, lung cancer

PUB134 REPEATABILITY ANALYSIS OF GTV TEXTURE FEATURE EXTRACTED FROM FOUR-DIMENSIONAL CT IN NSCLC
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Background: Objectively and reproducibly quantify various imaging features is important to reveal the underlying biology of cancer. In this study, we assessed the repeatability of GTV texture feature extracted from four-dimensional CT (4D-CT) in NSCLC patients. Methods: Five NSCLC patients scanned by 4D-CT were consecutively enrolled in this research. For each patient, GTV was delineated manually in each phase of the 10 four-dimensional CT phases and agreed by two observers. 9 kinds of texture features, including angular second moment, inertia, inverse difference moment, entropy, correlation, sum average, difference average, sum entropy, difference entropy were extracted from the GTV for each phase based on gray level co-occurrence matrix. Interclass Correlation Coefficient (ICC) analysis was performed to quantify the reproducibility of a feature. The ICC value of 0.85 was considered a reproducible feature. Results: The features were found to have little dependency on the phases of 4D-CT. Most texture features were found to have significantly higher reproducibility (ICC = 0.89±0.013, p<0.001) except sum average (ICC = 0.75±0.21, p<0.001). Conclusion: The study shows most texture features are repeatable between different 4D-CT phases in NSCLC. However, the reproducibility of radiomics features (including texture features) causing by different reconstruction algorithms and the slice thickness, should be further study to reveal the underlying biology of cancer.

Keywords: NSCLS, texture feature, radiomics feature, four-dimensional CT

PUB133 THE INVESTIGATION ON SHANGHAI LOCAL LUNG CANCER PATIENTS’ PROGNOSIS AT SHANGHAI CHEST HOSPITAL: 2004-2014
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Background: This research investigates the prognosis of Shanghai local lung cancer patients who were treated at Shanghai Chest Hospital from 2004 to 2014. Methods: This research first identifies Shanghai local lung cancer patients with their address and resident ID information recorded in hospital’s information system, and then categorizes patients into various pathology/cancer stage groups, based on their diagnosis codes. With collected data, this study calculates patients’ survival rates with Kaplan-Meier method and draws survival curves. Cox risk regression model is also employed to identify factors with significant impact on patients’ overall survival. Results: From January 1, 2004 to December 31, 2014, 21,918 Shanghai local lung cancer patients were treated at Shanghai Chest Hospital. Among all these patients, 10,646 were investigated, including 2,019 cases of squamous cell carcinoma; 5,949 cases of adenocarcinoma; 437 cases of adenosquamous carcinoma; 593 cases of small cell lung cancer; 125 cases of large cell carcinoma; and 583 cases of poorly differentiated carcinoma. According to the stage of their cancers, 3.4% patients were at stage I; 26% were at stage II; 29.3% were at stage III; and 64.7% at stage IV. Among these investigated cases, 7,617 patients died and 3,029 cases were censored. This study finds that small cell lung cancer, squamous cell carcinoma, and poorly differentiated carcinoma have the poorest prognosis. Stage IV adenocarcinoma patients have better prognosis than stage IIIb patients of aforementioned cancers. Female patients have better prognosis than male patients in the cases of adenocarcinoma, small cell lung cancer, and poorly differentiated carcinoma (p<0.05). In this investigation patients are also categorized into 2004-2006, 2007-2010, and 2011-2014 groups. This research finds that after 2011 adenocarcinoma cancer patients have significantly improved prognosis (p<0.05). However, there is no significant improvement among other cancer types. This study also finds that among patients surviving for more than five years, stage IV patients have the highest percentage (adenocarcinoma 37.58%; squamous cell carcinoma 8.15%; poorly differentiated carcinoma 5.61%; and small cell lung cancer 4.42%). The five year survival rates of these patients are, respectively, 7.0%, 6.1%, 2.5%, and 5%. Conclusion: Adenocarcinoma patients have better prognosis than the patients of other types of cancers.

Keywords: Lung neoplasms, Prognosis

PUB135 LEAF INTERDIGITATION CAN IMPROVE THE PLAN QUALITY FOR MULTIPLE ISOLATE TARGETS NSCLC SLIDING WINDOW IMRT PLANS IN MONACO TPS
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Background: The purpose of this study was to experimentally assess the dosimetric impact of leaf interdigitation for NSCLC sliding window IMRT (dMLC) plans in Monaco TPS. Methods: 20 NSCLC patients (one to four isolate targets) previously treated were re-planned for dMLC with and without leaf interdigitation. Elekta synergy linear accelerator was used in this study. The treatment plans were evaluated on the following dosimetric variables: conformity index, homogeneity index and the normal lung sparing. Results: For one isolate target, the plan quality was equivalent with and without leaf interdigitation (p>0.05). For multiple targets, leaf interdigitation could improve the conformity index obviously (p<0.05). Meanwhile, leaf interdigitation showed well sparing for the normal lung (p<0.05). Conclusion: The study shows that leaf interdigitation can improve the plan quality for multiple isolate targets NSCLC dMLC plans in Monaco TPS.

Keywords: Leaf interdigitation, sliding window IMRT, NSCLC

PUB136 EFFECT OF PD-L1 TUMOR EXPRESSION ON CLINICAL BENEFIT OF PERSONALIZED DENDRITIC CELL BASED VACCINE IN PATIENTS WITH NON-SMALL CELL LUNG CANCER
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Background: The role of tumor PD-L1 expression in NSCLC is not clear. The study evaluated the correlation between PD-L1 expression and clinical benefit of personalized DCCV. Methods: 24 NSCLC patients treated in 2015 were enrolled in this study. The non-small cell lung cancer (NSCLC) tumors were stained for the PD-L1 protein using an automatic immunostaining system, and PD-L1 expression was visually scored using a semi-quantitative method. The patients were scored as PD-L1 positive or PD-L1 negative. Results: The mean age of the patients was 60.1±10.3 years; 18 (75%) were male. 14 patients had adenocarcinoma; 5 had squamous cell carcinoma; and 5 had large cell carcinoma. The five year survival rates of these patients are, respectively, 37.5%, 12.5%, and 12.5%. Conclusion: The study shows that PD-L1 expression is associated with the clinical benefit of personalized DCCV.

Keywords: PD-L1, NSCLC, DCCV, clinical benefit.
Abstracts

Background: Modern antitumor vaccination therapy is evidence-based and one of the most promising strategies in lung cancer biotechnology today. Earlier, promising results from phase III trial of dendritic cell-based vaccine immunotherapy in IIB-IIIA stage non-small cell lung cancer (NSCLC) patients have been obtained by National Cancer Institute of Ukraine. It’s known, the PD-1/PD-L1 pathway may play an important role in blunting immune response to tumor vaccines. However, the predictive value of PD-L1 tumor expression is controversial. We speculate that tumor dendritic cell (DC)-vaccine will have more benefits in NSCLC with low PD-L1 tumor expression. Therefore, our main goal is to examine the clinical benefit of personalized DC-vaccine therapy in NSCLC patients according to PD-L1 tumor expression. Methods: Original construction of DC-vaccine has been used: autologous DCs of monocytic origin loaded with mechanically heterogenized microparticles of tumor cells. The surface state and functional activity of DCs were evaluated by the expression of cell surface markers C8D3/86 and HLA-DR, TNF-a, CD80, TGF-b, IL-10, CCR7 and IL-12 p35/p40 mRNA level as well as bioactive IL-12/70 IL-12 protein content. DC in amount 4,62±0,37x10^6 per injection were injected intravenously in 1-3 courses with 6 months interval. One course consisted of 5 injections with one-month interval. Clinical and immunological monitoring of DC-vaccine therapy was performed. PD-L1 gene expression level was detected in primary tumors by real-time RT-PCR. Results: Tumors were categorized into groups according to high and low PD-L1 expression levels based on cutoff point - optimal criterion that was determined by ROC analysis (AUC=0.79, p<0.03). Sensitivity and specificity of PD-L1 gene expression as predictive biomarker for NSCLC patients received DC-vaccine therapy were 75% and 83%, respectively. Cox proportional hazard regression analysis revealed that PD-L1 gene expression level has no significant effect on 5-year overall survival (OS) rate for NSCLC patients but has a significant impact on 5-year event-free survival (EFS) of patients. Lower level of PD-L1 gene expression correlates with a significant increase in EFS (p=0.026). The 2-year EFS rate for patients with low PD-L1 gene expression was 86% compared to 29% for high expression (F-Cox criterion: F=4.68, p=0.017). Conclusion: PD-L1 tumor expression is a predictive significant biomarker to personalized DC-vaccine therapy. The identification of such possible predictive markers is crucial for the rational development, research and advance of combined immunotherapy and to guide the optimal choice of immunotherapy combinations schemes. Obtained results might be background for new therapy schemes which based on the anti-PD-1 inhibitor and specific immunotherapy.

Keywords: PD-L1 tumor expression, combined immunotherapy, dendritic cell vaccine, non-small cell lung cancer

PUB137 LUNG CANCER IN YOUNG PATIENTS: HIGHER RATE OF DRIVER MUTATIONS, BRAIN INVOLVEMENT AND BETTER SURVIVAL

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Background: Young patients with lung cancer represent a distinct subset of patients with this disease. Studies show that younger patients are more likely to be women and non-smokers. They are diagnosed at a later stage; the histologic type is more likely to be adenocarcinoma and more driver mutations such as in the EGFR gene are found. Prognosis and survival of the younger patients has mostly been shown to be better in the younger population. Methods: Retrospective data was collected in a single tertiary hospital between 1/2010 and 12/2015. Patients were divided into 2 age groups: patients who were diagnosed aged younger than 50 years and patients aged older than 60 years. We analyzed demographic characteristics, disease course and survival. Results: The younger cohort included 77 patients, with a median age of 45 years. The older group included 107 patients, median age of 68 years. Both groups had similar female to male ratio and had similar ratio of smokers, although the younger had significantly lower median pack years (40 vs. 60, P<0.001). Adenocarcinoma was the most common histopathology in both age groups (64% vs. 71%) and a larger proportion of small cell lung cancer histology was found in the younger cohort (12% vs. 3%, P<0.001). EGFR mutations were more common in the young cohort (18% vs. 13%, P=0.06), as well as ALK translocations (9% vs. 1%, P=0.001) and accordingly, they were treated by more targeted therapies (25% vs. 16%, P=0.015). Although young patients had more brain metastasis (38% vs. 21%, P=0.002), their median survival was not significantly different than the older cohort (24.8 vs 18.2 months p=0.5). yet after performing sub-stratification it was found that patients under 40 years had better median survival (70.8 months P=0.05). Among patients with a driver mutation, median survival was better for younger patients (31.9 vs. 17.0 months, P=0.003). Conclusion: Young patients with lung cancer have better median survival; their tumors harbor a higher rate of driver mutations and they have a higher percentage of brain involvement.

Keywords: Younger Patients, Driver Mutations, personalized medicine, lung cancer

PUB138 STAT6 IS A POTENTIAL MARKER FOR DIAGNOSING PULMONARY ADENOCARCINOMA FROM SQAMOUS CELL CARCINOMA

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Background: Histologic distinction among non-small cell lung carcinomas, particularly between squamous cell carcinoma (SQC) and adenocarcinoma (ADC), has become more important. Recently, we found a gene named signal transducer and activator of transcription 6 (STAT6) to be a potential specific marker for ADC trough cancer browser at UCSC. Methods: STAT6 expression was evaluated in total 1047 primary lung carcinomas, including 509 SQCs and 538 ADCs. In the human pathological array, significant results showed. Results: STAT6 expression was significantly higher in ADC than compared to SQC (P<0.05). Detailed gene distributions of STAT6-positive cases were as follows: 357 (66.4%) of 538 SQCs, 117 (23%) of 509 ADCs. STAT6 histological staining yields high sensitivity as well as high specificity for distinguishing ADC from SQC. Conclusion: STAT6 is a potential marker for diagnosing pulmonary adenocarcinoma from squamous cell carcinoma.

Keywords: marker, Adenocarcinoma, Squamous cell carcinoma, STAT6

PUB139 ASSESSING PEOPLE’S PERCEPTION REGARDING PICTORIAL PACKAGING OF CIGARETTE PACKETS IN BANGLADESH

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Background: Currently the prevalence of smoking in Bangladesh is high (43.3% of the total population) and Bangladesh Government is committed to curb the usage of tobacco in the country. According to the newly amended law (2013), health warning shall be printed on top of both sides of the packets of all tobacco products covering at least 50% of the display area. A study was conducted to assess the perception of smokers and non-smokers regarding the health warning and the impacts of the new pictorial packaging in Bangladesh. Methods: Qualitative and quantitative both methods were used to conduct the study. 25 current smokers and 25 non-smokers participated as respondents and a semi structured questionnaire was used to conduct the study. Also, total five cigarette packets which contain pictorial warnings which are available in Bangladesh were shown to the respondents and they were asked to express their perception about the new packaging. Results: 21 smokers and all 25 non-smokers said these pictorial packaging looks dreadful and non appealing. 8 of the current smokers expressed their interest in quitting smoking and they stated these pictorials creating negative impacts in their mind. Therefore, the current smokers said pictorial packaging would be very effective for the teenagers who started smoking lately. On the other hand, out of 25 non-smokers, 19 answered they believe these pictorial packaging would help the government to lower the smoking rate. Also, they said people would be more aware about the harms of tobacco and conscious on using tobacco products. All of the non-smokers said, after watching these packaging they would never use any form of tobacco. The non-smokers added, not only pictorial packaging, tobacco taxation would also help the government to decrease the smoking rate, however, 12 of the current smokers also agreed with the statement. Conclusion: Both the smoker and non-smoker respondents of the study agreed that the pictorial packaging is creating a negative impact in people’s mind and both the smokers and non-smokers stated it would frighten the teenagers who are planning to start smoking. Both of them agreed, Bangladesh government is implementing it’s law strictly regarding the pictorial packaging.

Keywords: Pictorial packaging, Bangladesh

PUB140 A PILOT STUDY TO ASSESS CIRCULATING TUMOR CELLS, CIRCULATING TUMOR CELL DNA AND CELL FREE DNA IN PATIENTS WITH SMALL CELL LUNG CANCER

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Background: Small cell lung cancer (SCLC) is a highly aggressive malignancy with median survival of 18 months. Due to this reason it has been difficult to make standard care recommendations. The lack of standard therapy for localized disease and metastatic disease has resulted in the development of new treatment strategies. The assessment of disease is currently difficult due to the small size of tumor burden and difficulty in accessing tumor from distant metastases. Circulating tumor cells (CTCs), circulating tumor cell DNA (ctDNA) and cell free DNA (cfDNA) provide an opportunity for easy and frequent monitoring of the tumor burden. Methods: Patients with histologically confirmed small cell lung cancer were recruited from Memorial Sloan Kettering Cancer Center, New York. A total of 20 patients were included in the study. A blood sample was collected from each patient and the samples were subjected to CTC, cfDNA and ctDNA analysis. The CTC was done using CellSearch system. The ctDNA was extracted using the QIAmp DNA Blood kit (Qiagen) and the cfDNA was extracted using the MagNa Pure system (Roche). Results: 12 patients had small cell lung cancer and 8 patients had other malignancies. The CTC results were obtained for only 14 eligible patients. Out of 7 patients, 2 patients had low CTC count (2<CTC count<4) and 5 patients had high CTC count (CTC count>4). Out of 7 patients, 2 patients had low ctDNA concentration (ctDNA concentration<10) and 5 patients had high ctDNA concentration (ctDNA concentration>10). The cfDNA concentration was high for all patients. Conclusion: This study shows that CTC, ctDNA and cfDNA can be assessed in SCLC patients. Further studies are needed to assess the role of CTC, ctDNA and cfDNA in the assessment of SCLC treatment response and recurrence.

Keywords: Circulating tumor cells, Small cell lung cancer, Circulating tumor cell DNA, Cell free DNA, SCLC
Background: There are limited data on the genomic landscape of Small Cell Lung Cancer (SCLC), often limited by access to large biopsies. We sought to characterize the molecular profile of patients with relapsed and refractory SCLC (R/R SCLC) using circulating tumor cell (CTC) DNA and cell free DNA (cfDNA). Methods: Blood samples (7.5 ml for CTC enumeration and 10 ml for cfDNA isolation) were prospectively collected from patients with R/R SCLC at the time of documented progression. CTC were enumerated using CellSearch®. Next generation DNA sequencing (NGS) was carried out on CTC DNA, cfDNA and matched archived tumor biopsies using two panels, i.e. Personal genome diagnostic panel; (PGDx PlasmaSelect™) with 63 genes, and ii. Custom panel with 90 genes. Results: Twelve patients with R/R SCLC were enrolled (3 male, median age 63 years, 2 limited stage at diagnosis, 33% platinum-refractory). There was no association of CTC count with survival or disease stage at diagnosis. A positive association was seen between CTC count and quantity of cfDNA (Pearson’s correlation = 0.77, p = 0.0091). Multiple genetic alterations were identified from CTC DNA and cfDNA, including mutations in p53, Rb and gene amplification of the c-Myc, which are the most frequent genetic alterations reported in SCLC. Using PGDx PlasmaSelect panel, genetic alterations were identified in 11/12 patients from cfDNA and 9/12 patients from CTC DNA. Mutations in DNM34, AR, KIT, ATM and PIK3CA each were seen in ≥3 patients. Additional somatic mutations including APC, NOTCH3, SYNE1, CREBBP, ATRX were identified using the custom panel, in 9/12 from cfDNA and 8/12 from CTC DNA. The most common mutation across both tissue samples was p53 mutations. Concordance was noted to be higher for mutated genes in tissue samples with higher allelic frequency (AF ≥ 1%, concordance rate ~ 10%, AF ≥ 20%, concordance rate ~ 29%). Conclusion: Data from this pilot study demonstrate that it is feasible to use cfDNA and CTC for characterization of known genetic alterations in SCLC patients. Larger studies are needed to define its use in the clinical setting. Such approaches may ultimately prove useful in identifying prognostic, predictive and resistance biomarkers.

Keywords: gene sequencing, circulating DNA, cell free DNA, small cell lung cancer

PUB141 FINANCIAL IMPLICATION OF LUNG CANCER TREATMENT IN AN AGERGANIAN NICIAL FACILITY

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Background: The cost of treating individuals with lung cancer is huge and families usually seek financial support from various sources. Methods: In this study, 80 patients with lung cancer between January 2009 and December 2013 for tobacco cessation were interviewed in a Nigerian de-addiction center Inclusion Criteria: 1) Participants are on tobacco cessation program and have been abstinent for at least 6 months; 2) Diagnosis of lung cancer by self-reports, supplemented physician’s report. Measures: Demographic information was collected including cost and source of treatment in a 28 day period. Ethical and consent obtained Statistical analysis: ANOVA and t test were used in the analyses, at 95% CI, p < 0.05 using the (SPSS version 16.0). Results: Table 1: Sociodemographic Characteristics

<table>
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</table>

Conclusion: In the current sample, there were no demographic differences in cost of treatment. None of the client has support from any health insurance program and over half borrowed money from any financial institution or sold their properties. There is an urgent need for advocacy programs for lung cancer patients in Nigeria.

Keywords: lung cancer, cost, treatment

PUB142 FEAR OF CANCER RECURRENCE IN EARLY STAGE LUNG CANCER PATIENTS

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Background: Fear of cancer recurrence (FCR) is one of the most distressful experiences among advanced lung cancer (LC) patients. It has found to impact patients quality of life. However, limited investigations have explored patients’ concerns about FCR in early stage LC populations who are expected to have relatively much longer survival time. Thus, the purposes of this study are: (1) to examine the level of FCR in early stage lung cancer patients at three months post surgery, (2) to explore patients’ coping strategies dealing with FCR, (3) to examine the relationship among severity of FCR, depression, anxiety, and disease stages (Ia vs. Ib, II, IIIa) .

Results: A cross-sectional survey with consecutive sampling was conducted in a medical center in Northern Taiwan. Eligible patients were those newly diagnosed early stage LC patients (stage I, II, IIIa) and three months post surgery. We used the Fear of Cancer Recurrence Inventory (FCRI) to examine FCR and their coping strategies. Patients’ depression, anxiety (by Hospital Depression Anxiety Scale), disease information were assessed. Patients were assessed by two trained research nurses after the approval of IRB and patients’ consent. Methods: A cross-sectional survey with consecutive sampling was conducted in a medical center in Northern Taiwan. In general, most early stage LC experience mild level of FCR. However, about 10 % of patients reported to experience moderate level of FCR. About 640% of patients reported the FCR experiences were easily triggered by seeing or hearing television or newspaper about cancer. Patients with higher FCR also have higher depression and anxiety. Patients with stage Ib have significantly lower FCR concerns compared to those with stage IIb, II and IIIa. For coping strategies, about half of LC patients convinced themselves that everything would be fine or to think positively to cope with this distressful concern. There were one fourth of patients went to hospital
for physical check up to prevent possible cancer recurrence. Conclusion: In this study, FCR is still a concern and even in a moderate level for early stage LC patients in three months after surgery. Health care professionals should help them manage this distress would be strongly recommended.

Keywords: early stage lung cancer, Fear of cancer recurrence, depression, anxiety

PUB143 ENVIRONMENTAL TOBACCO SMOKE AS A RISK FACTOR TO INCREASING RESPIRATORY CHILDHOOD INFECTION AND PNEUMONIA IN SOUTH WEST REGION NIGERIA

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Background: There is consistent evidence that children exposed to environmental tobacco smoke (ETS) have higher incidence of asthma, ear and throat disease, worsening of asthma symptoms and lung symptoms as cough, wheezing and pneumonia. A child exposed to ETS has about 30% higher risk of absence from school due to illness. Evidence clearly implicates (ETS) as a cause of lung cancer, excess respiratory disease, and cardiovascular disease mortality in nonsmokers. Few studies have looked at the interaction of tobacco use or ETS exposure with occupational and ambient air pollution (both indoor and outdoor) in contributing to chronic obstructive pulmonary disease (COPD) in developing countries, or the importance of ETS as a risk factor for the already high burden of childhood respiratory infections. Methods: A descriptive cross sectional study was carried out in 5 states (Ogun, Lagos, Akure, Oyo and Ekiti). A multistage cluster random sampling was employed to select 450 families in each state. Data was collected using structured questionnaires by trained interviewers. Results: About 2113 records were available for analysis. There were 1298(60.7%) males and 815(38.1%) females aged 10 and below. A Majority, 807(38.0%) live with both parents, 213(10.0%) live with mother alone while 265(12.5%) live with relatives. The prevalence of children exposed to ETS in the southwest region Nigeria was 72.2%, the study further revealed that 28.5% of children in this region with respiratory childhood infection are exposed to environmental tobacco smoke and 18.4% pneumonia cases are attributed to ETS. However, (122, 14.7%) parents or relatives don’t see a problem with using tobacco products. It is also clearly stated that about 46.9% cases of respiratory childhood infection and pneumonia combined are caused by ETS in the south west region Nigeria. Conclusion: Since Environmental Tobacco Smoke has this much negative effects on children in the south west region Nigeria. Efforts should be tailored towards protecting children from ETS to reduce the rate of children exposed to ETS, thereby bringing or reducing respiratory childhood infection and pneumonia in Nigeria

Keywords: Tobacco Control, children, Environmental tobacco smoking

PUB144 ROLE MODELS “A TOOL FOR EFFECTIVE TOBACCO CONTROL CAMPAIGN”

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Background: Each day, nearly 6,000 children under 18 years of age start smoking; of these, nearly 2,000 will become regular smokers. That is almost 800,000 annually. Approximately one half of continuing cigarette smokers will die prematurely from tobacco use; this is mostly after several years or more of excess disease and disability. Methods: Experience has showed that adolescent and youths all over the world especially Nigeria are attracted to tobacco of any form. Role Models will be used through the help of the media and the entertainment industries to give a tobacco control sensitization talk for two minutes each on a video that will be televised. This video will also be uploaded on “Facebook”, Twitter, WhatsApp and “YouTube” for a wider viewing of this campaign; these role models are mentors to many others in Africa. Results: These methods will creatively increase the awareness level of young people in Nigeria and Africa on the harmful effect of tobacco smoking and promote the campaign against tobacco smoking. The methods will also reduce the rate of youth smoking in Nigeria and Africa, as some of these role models are also models to many youths in other African countries. Conclusion: Evidence has showed that some of these role models are used as a campaign tool by the tobacco industry in Nigeria and other countries. It is therefore systemic and appropriate to use the same method to reduce the current upsurge in youth smoking and cancer related disease in Nigeria and Africa.

Keywords: Role model, Tobacco Control, youth

PUB145 THE ANEUPLOIDY OF INOCULATED CELL CULTURE OF LLC UNDER THE INFLUENCE OF N-HYDROXY-4-(((E)-2-PHENYLETHENYL)SULFONYL)AMINO)BUTANAMIDE

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Background: Aneuploidy is a common feature of human solid tumors, often associated with poor prognosis. The oncogenic signaling pathways, which are universally dysregulated in cancer, contribute to the promotion of aneuploidy. Based on this goal in our work we determined the level of aneuploid and diploid cells of LLC under the influence of N-hydroxy-4-(((E)-2-phenylethenyl)sulfonyl)amino)butanamide (NHPSAB) in vitro and in vivo. Methods: The primary culture was obtained from transplantable Lewis lung carcinoma after 2.2 times trypsinization of tumor tissue in trypsin EDTA solution with pH 7.0 (Sigma, USA). Cell cultivation was conducted under the standard conditions in RPMI medium and 10% FBS (Sigma, USA) at 37°C, 100% humidity and 5% CO2. Modified hydroxamic acid NHPSAB was added to the exponential and stationary growth phases. After cultivation the number of living cells was determined by MIT colorimetric test and cell counts were performed by trypan blue. Metastatic volume in lung was assessed by determining the linear dimensions of metastases of C57BL/6 mice. Results: The study was shown that the level of aneuploid cells decreased - 37.1± 3.2 and the level of diploid cells increased - 62.4 ± 3.8 compared with control - 59.2±1.7 and 40.8±1.6 respectively. The results were obtained the different patterns of metastases in lungs in vivo. Conclusion: Our results show that NHPSAB causes a decrease in the number of aneuploid and increase diploid cells in vitro, and reduce the number of metastases in the lungs in vivo.

Keywords: LLC cell line, aneuploid, diploid, hydroxamic acid's

PUB146 PROGNOSTIC PREDICTION OF PEMETREXED-PLATINUM CHEMOTHERAPEUTIC REGIMEN BY SERUM METABOLOMICS

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1Peking University peking Tonghua Center for Life Sciences, Academy for Advanced Interdisciplinary Studies, Beijing/China, 2Cancer Hospital Chinese Academy of Medical Sciences, Beijing/China

Background: Lung cancer is a leading cause of cancer deaths worldwide and chemotherapy is the major treatment for advanced stage patients. Currently, pemetrexed combined with platinum (PC regimen), due to its promising efficacy and a favorable toxicity profile, has become a standard schedule as the first-line treatment for advanced non-squamous NSCLC. Nevertheless, like all chemotherapeutic regimens, drug resistance inevitably limits the efficiency of this preferred cytotoxic drug combination. In virtually all initial responders rapidly develop acquired resistance. Besides, some cases are intrinsically resistant to this chemotherapeutic regimen, and the disease progression at the first radiological assessment of response after one or two cycles of treatment. Metabolomics, by testing the holistic low-molecular-weight organism metabolites, offers an appropriate strategy to studies of pathophysiological processes, interaction of environment and genotype, drug toxicity and efficacy, biomarker discovery and so on. Metabolites play a substantial role in biological systems. Being the closest biological proximity to the phenotype of the system, metabolomics allows rapid observation of responses to system perturbations in the metabolome. In this work, we hypothesis that the metabolic characteristics of serum may associated with the inherent response (resistance or sensitivity) of patients to cytotoxic drugs. Methods: In this study, we performed liquid chromatography coupled to mass spectrometry (UPLC-MS) analytical platform was applied to perform the metabolic profiling studies of serum samples, aiming to find metabolic biomarkers which could predict the benchmark of pemetrexed and platinum treatment in adenocarcinoma NSCLC patients. Results: In the retrospective study, serum samples were subjected to the untargeted metabolic analysis. The results clearly indicated the different patterns of metabolomics profiles in accordance with the clinical outcomes of progressive disease (PD) or partial response (PR). We then established a prediction model consisting of a robust metabolites-pattern that can predict the response of chemotherapy-naive NSCLC patients before receiving PC chemotherapy regimen. And in prospective study, we employed this new method to select the patients who are more likely to benefit from PC regimen, and gave suggestions to take an alternative chemotherapy regimen to the patients who might not sensitive to the PC regimen according to our investigation. The metabolic alterations in serum before pemetrexed and platinum chemotherapy regimen are associated with clinical benefit. This study offers a validated method to identify patients who are unlikely to respond to this treatment and thus can be offered alternative treatments or entry into clinical trials.
Keywords: prognostic prediction, NSCLC, chemotherapy, metabolomics

PUB147 KRAS MUTANTS REGULATED PD-L1 EXPRESSION THROUGH NF-κB AND HIIF-1α PATHWAYS IN NON-SMALL CELL LUNG CANCER CELLS
Rong Guo, Jie Wang, Hua Bai
Cancer Hospital Chinese Academy of Medical Sciences, Beijing/China

Background: KRAS is one key driving gene for tumorigenesis of lung cancer and plays an important role in EGFR/TKIs resistance. To investigate the molecular mechanism of the expression regulation of PD-L1 by mutant KRAS gene in NSCLC cells, we had pursued researches as described below. Methods: The expression of PD-L1 and downstream signaling molecules of KRAS gene, including p-AKT, p-ERK, p-ικκand HIF-1α, in 13 NSCLC cells were examined by Western blot. Additionally, two NSCLC cells, H292 and H661, were transfected with various KRAS mutants and treated with MEK/ERK inhibitor U0126, PI3K/ AKT inhibitor LY294002, and NF-κB inhibitor BAY117082, respectively, and further examination of the expression of PD-L1 and key signaling molecules of KRAS pathway by Western blot was carried out. Results: The significantly positive correlation between expression levels of PD-L1 protein and p-ικκ as well as HIF-1α-proteins in 13 NSCLC cells. Furthermore, MEK/ERK and PI3K/ AKT/mTOR all participated in the process of up-regulated PD-L1 expression by KRAS mutants in both H292 and H661 cells. Notably, the variation tendency of p-ικκ expression and especially HIF-1α showed strong consistency with PD-L1 in both H292 and H661 cells treated with KRAS mutants and the three kinds of inhibitors. Conclusion: Our findings revealed that KRAS mutants regulated PD-L1 expression through NF-κB and HIIF-1α pathways in NSCLC cells, and suggested the correlation between EGFR/TKIs resistance and immune escape as well as significance of combined treatment of target therapy and immunotherapy in NSCLC.

Keywords: KRAS, PD-L1, HIF-1α, NSCLC

PUB148 EFFICACY OF HEIMLICH VALVE IN PREVENTING AIR LEAKS
Amitesh Khare
Thoracic Surgery, Emory University School of Medicine, Atlanta/GA/United States of America

Background: One of the most common complications after a lung reduction surgery is prolonged air leak. This is a prospective study, which reports the routine use of Heimlich valve and its impact on total hospital stay and a reoperation for a persistent leak. This article evaluates a type of treatment for air leaks using Heimlich valves; the results also show a prospective algorithm for treatment of persistent air leaks.

Methods: From September 2005, through November 2011, 150 patients were operated for elective pulmonary resection, which had a heterogenous pattern of lung disease, with post operative mortality of 4 patients and average duration of total length of hospital stay of 10.61 days. Bilateral Heimlich valves were applied to 18 patients, and unilateral Heimlich valves in 132 patients. Dyspnea increased in 10 patients after switching to Heimlich valve and they were resumped on chest drainage with suction. Use of Heimlich valve was done irrespective of size of air leak. Grading of air leak, heimlich valve

Conclusion: Our results demonstrate that the Croton tiglium extract could inhibit the proliferation of A549 cells by regulating apoptosis in vitro. It has potential to provide biologically active compounds for treating NSCLC and deserves additional evaluation criteria as a new plant-derived anticancer agent.

Keywords: lung cancer, croton tiglium, apoptosis,MTT

PUB150 IGG4 RELATED LUNG DISEASE INVOLVING THE THORACIC VERTEBRAE
Michail Athanasopoulos1, Aspasia Antonopoulou2, Davide Patrini3, Efstratiou Koletsis4, Nikolaos Panagiotopoulos4, David Lawrence5
1University of Thessaloniki, Pireaus/Greece, 2Cardiothoracic Surgery, University of Patras, Patras/Greece, 3Thoracic Surgery, University College Hospitals, London/ United Kingdom

Background: Immunoglobulin G4-related disease (IgG4-RD) represents a recent inflammatory pseudotumor of the lung with high levels of IgG4. IgG4-RD is common in middle age males as an enlargement of one or more

Keywords: air leak, heimlich valve

PUB149 CROTON TIGLIUM EXTRACT INDUCES THE APOPTOSIS IN HUMAN LUNG CANCER A549 CELLS
Changyou Li, Xiao Wu, Rongli Sun, Peng Zhao, Fengjuan Liu, Chunling Zhang
Qingdao Central Hospital; Qingdao/China

Background: Croton, a large genus of Euphorbiaceae, is widely distributed in tropical regions of South-East Asia and China. Many researchers previously reported the pharmacological and physiological actions of Croton species on anti-inflammatory, anticonvulsant and wound healing properties. Mature Croton tiglium contains large amounts of natural medical components, in which croton alkaloid, flavonoids and diterpenes are anticancer agents. The study on application of Croton in lung cancer is lacking. In this study, we investigated the regulating effects of Croton tiglium extract on A549 cell proliferation and apoptosis.

Methods: Preparation of Croton tiglium seed extract. A549 human lung cancer cells culture Cell viability assay Flow cytometric analysis of apoptosis

Results: The MTT assay showed that Croton tiglium extract could exert a significant inhibitory effect on the proliferation of A549 cells. (Figure 1, P<0.05). It is notable that the highest proportion of early apoptotic cells were 45.94% with 100 μg/ml Croton tiglium extract treatment . (Figure 2, P<0.05).

Conclusion: One of the most common complications after a lung reduction surgery is prolonged air leak. This is a prospective study, which reports the routine use of Heimlich valve and its impact on total hospital stay and a reoperation for a persistent leak. This article evaluates a type of treatment for air leaks using Heimlich valves; the results also show a prospective algorithm for treatment of persistent air leaks.

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Conclusion: Our results demonstrate that the Croton tiglium extract could inhibit the proliferation of A549 cells by regulating apoptosis in vitro. It has potential to provide biologically active compounds for treating NSCLC and deserves additional evaluation criteria as a new plant-derived anticancer agent.

Keywords: lung cancer, croton tiglium, apoptosis,MTT

PUB150 IGG4 RELATED LUNG DISEASE INVOLVING THE THORACIC VERTEBRAE
Michail Athanasopoulos1, Aspasia Antonopoulou2, Davide Patrini3, Efstratiou Koletsis4, Nikolaos Panagiotopoulos4, David Lawrence5
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Background: Immunoglobulin G4-related disease (IgG4-RD) represents a recent inflammatory pseudotumor of the lung with high levels of IgG4. IgG4-RD is common in middle age males as an enlargement of one or more

Keywords: air leak, heimlich valve
organ systems, mimicking malignancy and can be present simultaneously or metachronously. The fact that IgG4-RD lung disease can be asymptomatic with only abnormal imaging findings or can manifest with non-specific clinical symptoms can delay the diagnosis. Methods: A 41-year-old man was presented with subsequent back pain after rotator cuff injury. There were no signs in chest physical examination. In terms of medical history, he had a 20-pack year history of smoking and there was no relevant history. A computed tomography and a MRI of the chest and the abdomen was performed revealing a 3 cm right lower lobe paravertebral soft tissue density mass lesion, invading into the adjacent pleural surface with frank destruction of the right T6 costovertebral joint. The CT guided biopsy was not diagnostic. After multidisciplinary meeting, a right 3 ports VATS biopsy of the mediastinal mass was performed. The postoperative course was unremarkable. Results: The macroscopic description characterized by multiple fragments of firm dark brown and cream coloured nodular tissue. In terms of the microscopic description, sections of lung parenchyma and adjacent fibrous tissue showed a dense lymphoplasmatic infiltration predominantly located in the lung parenchyma with suggestion of obliterate phlebitis. The alveolar spaces showed occasional pneumocyte metaplasia with no atypia. Immunohistochemistry showed, inflammatory infiltration of CD138 positive plasma cells along with moderate amount of CD3 positive T-lymphocytes and scattered CD20 positive B-lymphocytes. Most plasma cells were express IgG and a large proportion of these are co-express IgG4. The IgG4 positive plasma cells, in areas were noted to amount up to more than 150 cells per field and amount up to more than 40% of the total plasma cells present. CK7 and TTF-1 highlight the pulmonary parenchymal architecture, which was in areas distorted due to marked inflammatory component. Serum IgG4 levels were also elevated (3.95 g/l) and overall IgG was within range of normality. A diagnosis of IgG4-related lung disease was made considering the lymphoplasmatic inflammatory infiltrate of the lesion, the laboratory findings and the radiological image. Conclusion: This case report demonstrated the existence of a posterior mediastinal IgG4-RD lesion extending to the adjacent pleural surface and vertebrae. To the best of our knowledge there has not been reported a similar case.

Keywords: IgG4-RD, lung, pseudotumor, IgG4

PUB151 THE INTRICATE MANAGEMENT OF THE EPITHELIOD HAEMANGIOENDOTHELIOMA

Michail Athanasopoulos, Aspasia Antonopoulou, Domniki Iatropoulou, Davide Patrini, Nikolaos Panagiotopoulos, Efstratios Koletsis, David Lawrence

1University of Thessaloniki, Piraeus/Greece, 2Cardiothoracic Surgery, University of Patras, Patras/Greece, 3University of Ioannina, Ioannina/Greece, 4Thoracic Surgery, University College Hospitals, London/United Kingdom

Background: Epithelioid haemangioendothelioma (EH) is a very rare tumor with vascular origin and an epithelioid or histiocytoid appearance. It originates from medium-sized or large veins. In this case the neoplasm thought to be a teratoma and diagnosed postoperatively as an epithelioid haemangioendothelioma with metaplastic bone formation and extra mediullary haematoepoiesis. Methods: Pulmonary function tests as well as Alpha-fetoprotein and Beta hCG were normal. A decision for a robotic excision of the mediastinal mass was made. The procedure was uncomplicated/successful. Results: Macroscopical examination revealed an anterior mediastinal mass covered by adipose tissue contained separate lymph nodes with no lymphovascular invasion, weighting 75g and measuring 72 x 50 x 38mm, with infiltrated areas and calcification. Microscopic examination showed fibro fatty tissue that was diffusely infiltrated by a cellular tumor. The tumor was characterized as uncapsulesd, with poorly defined margins and with a predominant cell population of large epithelioid and spindled-shaped cells. These cells formed nodular areas and contained a glassy cytoplasm, which was in areas vaculated and a prominent pseudonuclear inclusion. There was a low mitotic count and a low proliferative index (Ki67: <5%). Immunohistochemistry demonstrated that these cells expressed the vascular markers CD31 and CD34. Mixed with these cells some osteoclasts were observed as well as some metaplastic ossification. Some haematopoietic elements, haemosiderin laden macrophages, scattered haemosiderin as well as areas of sclerosis and occasional clusters of smooth muscle were also present. No tumor necrosis or mitotic figure was seen. Immunostains like S100, desmin, myogenin, SMA, desmin, myogenin, S100, Melan A, HMB45, MNF116, Cam5.2, chromogranin, synaptophysin, CD117, DOG1, EMA and GFAP were negative. Non-specific CD56 was present. Immunohistochemistry performed at RNOH showed that the tumour was diffusely positive for ERG. The pathological stage of the tumor was pT2bNxMx G1. Conclusion: Therapy of EH is difficult, because of the rarity. Surgery is a method that can be considered in unilateral single or multiple nodules. Interferon and chemotherapy containing the use of carboplatin and etoposide have been used in some cases. Bevacizumab, a monoclonal antibody against vascular endothelial factor (VEGF) has been also used in addition to chemotherapy in order to control the expansion of the tumor considering its vascular origin and the high expression of VEGF from it. Radiotherapy has been considered ineffective and has just been used to reduce the pain of bone involment. Regular follow up with no active therapy has been used for asymptomatic patients with diffuse lesions.

Keywords: chemotherapy, haemangioendothelioma, lung, mediastinal mass
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<td>Other (explain):</td>
<td>Fellow at Merck &amp; Co</td>
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<td>Ricardo</td>
<td>Avila</td>
<td>Stock Shareholder (directly purchased)</td>
<td>I am the founder and CEO of Accumetra, LLC. Accumetra develops phantoms and software to improve medical imaging decision making.</td>
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<tr>
<td>Mark</td>
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<td>Paul</td>
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<td>Bai</td>
<td>Other (explain):</td>
<td>Advisory board: Member of Clovis Oncology advisory board to discuss treatment practices in non-small lung cancer, therapy efficacy, and safety profiles, Flince Research &amp; Design</td>
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<td>AbbVie, AstraZeneca, BMS, Boehringer Ingelheim, Clovis Oncology, Genoptix, Heat Biologics, Pfizer, Roche/Genentech, Seattle Genetics, and Trovagene</td>
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<td>Other (explain):</td>
<td>I am an employee of Analysis Group. Analysis Group has received funding from Novartis to partner on this study. Ceritinib is Novartis' product.</td>
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</tr>
<tr>
<td>Hossein</td>
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<td>Lilly, Bristol-Myers Squibb, Clovis, Genentech, Pfizer</td>
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<tr>
<td>Hossein</td>
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<td>Grants/Research Support</td>
<td>Millenium (institution)</td>
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<td>BMS, Celgene</td>
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<td>Hossein</td>
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<td>Other (explain):</td>
<td>(Travel, Accommodations, Expenses): BMS, Lilly, Genentech, Clovis</td>
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<tr>
<td>Diana</td>
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<td>Honoraria</td>
<td>Advisory board for Novartis / Boeringher Ingleheim / AstraZeneca / MSD</td>
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<tr>
<td>Karin</td>
<td>Bowen</td>
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<td>McKesson Specialty Health</td>
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<td>Michael</td>
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<td>Astra Zeneca, Boehringer Ingelheim, Clovis, Roche, Genetech, Pfizer, Eli Lilly, Bristol Myers Squibb, Merck Sharpe and Dohme</td>
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<td>Brachmann</td>
<td>Full-time/part-time Employee</td>
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<td>Celgene Corporation</td>
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<td>Brada</td>
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<td>Jeffrey</td>
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<td>Varian, ViewRay Grant</td>
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<td>Bristol-Meyers Squibb (uncompensated), Celgene, Lilly, MedImmune/AstraZeneca</td>
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<tr>
<td>Julie</td>
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<td>(Contracted Research): Bristol-Meyers Squibb, MedImmune/ AstraZeneca, Merck</td>
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<td>Brahmer</td>
<td>Other (explain): Consulting Fees: Celgene, Lilly, Merck</td>
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<tr>
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<td>Other (explain): Non-Compensated Consulting: Bristol-Myers Squibb</td>
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<tr>
<td>George</td>
<td>Braileanu</td>
<td>Full-time/part-time Employee employee of Adelphi, the company paid by Amgen to conduct this study</td>
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<tr>
<td>Fadi</td>
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<td>Consultant Eli Lilly and Company</td>
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<tr>
<td>Fabrice</td>
<td>Branle</td>
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<td>Bredno</td>
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<td>Robert</td>
<td>Brody</td>
<td>Full-time/part-time Employee FT employee of AstraZeneca</td>
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<tr>
<td>Robert</td>
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<td>Dennis</td>
<td>Brown</td>
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<td>Alessio</td>
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<tr>
<td>Franz</td>
<td>Buchberger</td>
<td>Grants/Research Support Grants of Pharmaceutical Companies for the Work of Patient Advocacy Group</td>
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<tr>
<td>Raphael</td>
<td>Bueno</td>
<td>Honoraria Siemens Healthcare Diagnostics, Myriad Genetics, Inc.</td>
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<td>Other (explain): Siemens Healthcare Diagnostics, Myriad Genetics, Inc.</td>
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<tr>
<td>Paul</td>
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<td>Paul</td>
<td>Bunn, Jr.</td>
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<tr>
<td>Lea</td>
<td>Burke</td>
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<td>Thomas</td>
<td>Burke</td>
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<td>Donald</td>
<td>Bushnell</td>
<td>Grants/Research Support Critical Path Institute</td>
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<td>Lauren</td>
<td>Byers</td>
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<td>Lauren</td>
<td>Byers</td>
<td>Other (explain): Astex Therapeutics (Scientific Advisory Committee Member), AstraZeneca Pharmaceuticals (Scientific Advisory Committee Member), StemCentrx (Scientific Advisory Committee Member)</td>
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<td>Vincent</td>
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<td>Consultant Novartis, GSK, Astellas, Roche/Genentech, Lilly, Nanobiotich, Pfizer</td>
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<td>D. Ross</td>
<td>Camidge</td>
<td>Consultant Clovis Oncology</td>
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<td>D. Ross</td>
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<td>Grants/Research Support ARIAD Pharmaceuticals, Inc.</td>
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<tr>
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<tr>
<td>Meghan</td>
<td>Campo</td>
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<td>Paulo</td>
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<td>Full-time/part-time Employee Foundation Medicine</td>
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<td>Paulo</td>
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<td>Mireille</td>
<td>Cantarini</td>
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<td>FIRST NAME</td>
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<td>NATURE OF RELEVANT FINANCIAL RELATIONSHIP</td>
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<td>Xiting</td>
<td>Cao</td>
<td>Full-time/part-time Employee</td>
<td>Merck &amp; Co</td>
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<tr>
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<td>Cappuzzo</td>
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<td>David</td>
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<td>Consultant</td>
<td>Genentech</td>
</tr>
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<td>Astra Zeneca, Bayer Health Care, Biocopt, Biothera, Boehringer Ingelheim, Bristol Myers Squibb, Clovis Oncology, Genentech/ Roche, Guardant Health, Inviata, Janssen Diagnostics, Merck, Novartis, Pfizer, Teva Pharmaceuticals</td>
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<tr>
<td>Scott</td>
<td>Caroen</td>
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<td>EpicentRx, Inc</td>
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<td>John</td>
<td>Carpten</td>
<td>Other (explain):</td>
<td>Founder: Ashion Analytics, LLC</td>
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<td>Corey</td>
<td>Carter</td>
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<td>Bristol-Mys Squibb</td>
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<td>Silvio</td>
<td>Cavuto</td>
<td>Other (explain):</td>
<td>Biostatistician at Yghea Srl - Bologna - Italy, which is a CRO dealing with study design and statistical analysis for Roche.</td>
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<tr>
<td>Marie</td>
<td>Cawkwell</td>
<td>Full-time/part-time Employee</td>
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<tr>
<td>Fabiola</td>
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<td>Ceppi</td>
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<td>Robert</td>
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<td>Other (explain):</td>
<td>Intuitive Surgical, Ethicon, Community Health Systems, Myriad Genetics. Inc., Davol/BARD, Coviden/ Medtronic, KCI, an Acelity Company, Bovie Medical and C-SATS.</td>
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<td>Jamie</td>
<td>Chaft</td>
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<td>Chand</td>
<td>Other (explain):</td>
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<td>Jason</td>
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<td>Eli Lilly and Company</td>
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<td>Paul Ning-Man</td>
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<td>Stock Shareholder (directly purchased)</td>
<td>Bio-Cancer Treatment International Limited</td>
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<td>Busyamas Chewaskulyong</td>
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<td>Roche diagnostic company provide the cyfra test kit</td>
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<td>Marc Chiода</td>
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<td>Lucian Chirieac</td>
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<td>Consultant</td>
<td>Merck: advisory role</td>
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<td>Oana Chirita</td>
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<td>Christos Chouaid</td>
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<td>Other (explain):</td>
<td>In the past 5 years, Christos Chouaid received fees for attending scientific meetings, speaking, organizing research or consulting from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Hoffmann la Roche, Astra Zeneca, Sanofi Aventis, Lilly, Novartis, B</td>
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<td>Nadia Chouaki</td>
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<td>Eli Lilly and Company, Neullisy-sur-Seine, France</td>
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<td>Laura Chow</td>
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<td>Adept Field Solutions, Amgen, Bio Connections, Bionest, BioStrategies Group, BMS, KeyQuest, Navigant</td>
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<td>(travel, accomodations, expenses): Novartis, Merck</td>
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<td>Genzyme, Merck Sharp &amp; Dohme, Seattle Genetics</td>
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<td>Jared Christensen</td>
<td></td>
<td>Other (explain):</td>
<td>Riverain Technologies, LLC</td>
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<td>Daniel Christoph</td>
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<td>Other (explain):</td>
<td>travelling grants which I got from Roche.</td>
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<td>Fortunato</td>
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<td>Ciuleanu</td>
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<td>Advisory board and/or speaker: Astellas, Amgen, AstraZeneca, Bristol Myers Squibb, Janssen, Eli Lilly, Merck Sharp and Dohme, Pfizer, Roche, Boehringer Ingelheim</td>
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<td>J</td>
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<td>inVentiv Clinical/contractor for Pfizer</td>
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<td>James</td>
<td>Clark</td>
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<td>Stock Shareholder (directly purchased)</td>
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<td>Craig</td>
<td>Other (explain):</td>
<td>Founder: Ashion Analytics, LLC</td>
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<td>Jeffrey</td>
<td>Crawford</td>
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<td>Lucio</td>
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<td>Other (explain):</td>
<td>serves on advisory board of BMS, Boehringer Ingelheim, Pfizer during the conduct of the study</td>
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<td>Currow</td>
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<td>Mercedes Liliana</td>
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<td>I received honoraria as speaker and consultant in advisory boards and teaching activities related with lung cancer molecular test for Pfizer and Novartis</td>
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<td>Cheufou</td>
<td>Danjouma</td>
<td>Other (explain):</td>
<td>Proctor, I am Proctor thoracic robotic surgery</td>
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<td>Mads</td>
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<td>Other (explain):</td>
<td>I am founder, shareholder, and chairman of the board of directors in VAR2 Pharmaceuticals, which is the commercialization vehicle for VAR2-based therapeutics and diagnostics.</td>
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<td>The NELSON trial is supported by: ‘Zorg Onderzoek Nederland-Medische Wetenschapperen’ (ZonMW), ‘KWF Kankerbestrijding’, ‘Stichting Centraal Fonds Reserves van Voormalig Vrijwillige Ziekenfondsverzekeringen’ (RVVZ)</td>
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<td>LabCorp; myself; compensated. This is for post-marketing royalties from Dana Farber Cancer Institute owned intellectual property on EGFR mutations licensed to LabCorp.</td>
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<td>Other (explain): Co-owner of the Medycyna Praktyczna publishing company, involved in teaching of medical professionals and publishing medical journal and books</td>
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<td>Darius</td>
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<td>Lamman</td>
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<td>Guardant Health, Inc. With stock Ownership</td>
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<tr>
<td>Richard</td>
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<td>Other (explain):</td>
<td>Employee with stock ownership in Guardant Health, Inc.</td>
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<td>Stock Shareholder (directly purchased)</td>
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<td>Primo</td>
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<tr>
<td>E Jane</td>
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<td>AstraZeneca K.K., Bristol-Myers Squibb Company, CHUGAI PHARMACEUTICAL CO., LTD., DAICHI SANKYO COMPANY, LIMITED, Eli Lilly Japan K.K., Nippon Boehringer Ingelheim Co., Ltd., ONO PHARMACEUTICAL CO., LTD., TAIHO PHARMACEUTICAL CO., LTD.</td>
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<td>Paulina</td>
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<td>Paulina</td>
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<td>Stock Shareholder (directly purchased)</td>
<td>Pfizer Inc, Zoetic, Enteromedics, Nxstage Medical GE, Colgate Palmolive, 3M</td>
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<td>Lilly Oncology</td>
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<td>Lecia</td>
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<td>Consultant</td>
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<td>Other (explain): Founder and advisor for Jounce Therapeutics, (patent licensed): Jounce, BMS, Merck, Member of the Parker Institute for Cancer Immunotherapy at M.D. Anderson Cancer Center</td>
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<td>Advisory board or board of directors: Pfizer, Novartis, Genentech/Roche, ARIA, Blueprint, WXO, K5Q</td>
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<tr>
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<td>Frances</td>
<td>Shepard</td>
<td>Other (explain):</td>
<td>Prognostic and predictive gene signature for early stage NSCLC</td>
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<td>Stock Shareholder (directly purchased)</td>
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<td>PHE, my employer, provides consulting services for many healthcare companies</td>
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<td>Tomohide Tamura</td>
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<td>Boehringer Ingelheim, Bristol Myers Squibb, Chugai Pharma, Eisai, Lilly Japan, OncoTherapy Science, Inc., Ono Pharmaceutical, Taiho Pharmaceutical, Yakult Honsha</td>
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<tr>
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<td>Chugai, Novartis, BMS, Boehringer Ingelheim</td>
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<td>Michael Thomas</td>
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<td>Other (explain):</td>
<td>Serves on advisory board of BMS during the conduct of the study</td>
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<td>Caroline Tissing-Tan</td>
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<td>Sirtex Technology Germany GmbH</td>
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<tr>
<td>Victor</td>
<td>Velculescu</td>
<td>Other (explain): Founder of Personal Genome Diagnostics</td>
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<td>Victor</td>
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<td>Other (explain): On the Scientific Advisory Board of Ignyta</td>
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\*IT'S ABOUT TIME

VARGATEF\(^R\)  Abbreviated European Prescribing information. Please refer to local prescribing information as it may vary between countries. Different brand names are used in some countries. Presentation: Soft capsules, each containing 100 mg or 300 mg nintedanib as nintedanib hydrochloride, Indications: VARGATEF\(^R\) is indicated in combination with docetaxel for the treatment of adult patients with locally-advanced, metastatic or locally recurrent non-small cell lung cancer (NSCLC) of adenocarcinoma tumour histology after first-line chemotherapy. Posology and method of administration: 200 mg twice daily administered approximately 12 hours apart, on days 3 to 21 of a standard 21-day docetaxel treatment cycle. VARGATEF\(^R\) must not be taken on the same day of docetaxel. Adverse reactions may be managed by temporarily treatment interruption, dose reductions or permanent treatment discontinuation. Contraindications: Hypersensitivity to nintedanib, renal or or normal. or any of the excipients. Special warnings and precautions: Patients should be closely monitored for: gastrointestinal disorders, neutropenia and thrombocytopenia, haemorrhage, venous and arterial thromboembolic events. Dose prolongation. VARGATEF\(^R\) is not recommended in patients with predisposition to bleeding, anti-coagulant treatment, active brain metastases, and gastrointestinal perforation. Fertility. pregnancy and lactation: There is no data on the potential effects of VARGATEF\(^R\) on female fertility. Women of childbearing potential should be advised to avoid becoming pregnant and to use adequate contraception during and at least 3 months after the last dose of VARGATEF\(^R\). There is no information on the use of VARGATEF\(^R\) in pregnant women. Breastfeeding should be discontinued during treatment with VARGATEF\(^R\). Effects on ability to drive and use machines: Minor influence. Undesirable effects: Very common: neutropenia (including febrile neutropenia), decreased appetite, electrocardiographic abnormality, peripheral neuropathy, bleeding, diarrhoea, anorexia, nausea, abdominal pain, elevation in liver enzymes, increased heavy metal values in blood (increased iron, copper, calcium, magnesium, zinc, manganese), increased 

LUME-Meso: Phase III study of nintedanib + pemetrexed/cisplatin in patients with malignant pleural mesothelioma

A double-blind, randomised, global, multicentre, Phase III study of nintedanib in combination with pemetrexed/cisplatin, followed by continuing nintedanib monotherapy versus placebo in combination with pemetrexed/cisplatin, followed by continuing placebo monotherapy for the treatment of patients with unresectable malignant pleural mesothelioma (NCT01907100).

Main inclusion criteria
- Male or female ≥18 years of age
- Histologically confirmed epithelioid malignant pleural mesothelioma
- ECOG PS 0 or 1
- Measurable disease according to mRECIST criteria

Main exclusion criteria
- Previous systemic chemotherapy for malignant pleural mesothelioma
- Prior treatment with nintedanib or any other systemic therapy
- Patients with sarcomatoid and biphasic subtype malignant pleural mesothelioma
- Patients with symptomatic neuropathy
- Radiotherapy within 3 months prior to baseline imaging
- Patients who may be eligible to undergo surgical resection
- Active brain metastases
- Patients with mild-to-moderate renal insufficiency taking NSAIDs and unable/unwilling to interrupt treatment

Endpoints
- Primary endpoint: progression-free survival (PFS)
- Secondary endpoints: overall survival (OS) (key), objective tumour response evaluated according to mRECIST (modified Response Evaluation Criteria for Solid Tumors), disease control according to mRECIST

Progressive disease

For more information about the LUME Clinical Trial Program:

TALK: with a medical representative in the booth
EMAIL: MEDLUMEMesoTrial.ING@boehringer-ingelheim.com

ECOG PS=Eastern Cooperative Oncology Group performance status; IV=intravenous; NSAI=non-steroidal anti-inflammatory drug.
*On Days 2 to 21.
*Pemetrexed 500 mg/m² IV over 10 minutes on Day 1 of each 21-day cycle; cisplatin 75 mg/m² IV over 2 hours on Day 1 of each 21-day cycle.
*Treatment beyond progression is allowed if clinical benefit is perceived.

Nintedanib is being investigated in malignant pleural mesothelioma and is not approved. Nintedanib efficacy and safety in malignant pleural mesothelioma have to be fully established.

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4. Park K et al. Lancet Oncol. Published Online 12 April 2016.

*OS=overall survival; TTF=time to treatment failure.

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