2020 KALC International Conference

November 19(Thu) ~ 20(Fri), 2020
e-Conference

www.2020.kalcic.or.kr
Dear colleagues,

Welcome to the 2020 KALC International Conference Virtual!

We are honored to have you all at the 2020 KALC International Conference Virtual, hosted by the Korean Association for Lung Cancer (KALC), which will be held from November 19-20, 2020.

Building on the success of KALC 2018, the organizing committee has been working hard to bring you a program that addresses all the needs of lung cancer professionals. We invited world-renowned experts, and you will enjoy their lectures in the field of biology, pathology, diagnosis, as well as a state-of-the-art treatment of lung cancer. In addition to the abstract presentation, we also prepared interactive sessions and satellite symposiums, where the attendees can actively communicate with specialists on each vital topic.

We are confident that this academic event will offer the perfect platform for experts from lung cancer to exchange professional, scientific knowledge and valuable clinical experiences.

Considering the many challenges presented by COVID-19 and our objective of ensuring the health and safety of all attendees, we had to make an inevitable decision to make the event into a virtual conference.

Mainly, it will be an online streaming conference. Domestic speakers and panels will participate in an offline format to provide more realistic discussions and communications. International invited speakers will participate via online lectures and Q&A sessions, which have been arranged according to the time difference.

Although we cannot meet in person, we hope this new platform may provide a future method of maintaining our communication.

Once again, thank you for active participation at the 2020 KALC International Conference Virtual and have a valuable time interacting with one another during this academic event.

Best wishes to all of you!

Soon Hee Jung
President,
Korean Association for Lung Cancer (KALC)

Young Tae Kim
Chairman,
Korean Association for Lung Cancer (KALC)
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#### Organizing Committee

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Scientific Program Committee

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Dong Wan Kim                      Seoul National University Hospital, Korea

Secretary
Tae Min Kim                      Seoul National University Hospital, Korea

Members
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O Kyu Noh                       Ajou University Hospital, Korea
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Jong Mu Sun                     Samsung Medical Center, Korea
Sung yong Lee                   Korea University Guro Hospital, Korea
Sang Min Lee                    Asan Medical Center, Korea
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Jin Ho Choi                     National Cancer Center, Korea
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2. 전이성 비판형 비소세포폐암 환자의 1차 병용 요법 (KEYNOTE-407)
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4. PD-L1 1% 이상인 진행성 비소세포폐암의 2차 이상 단독요법 (KEYNOTE-010)
The PACIFIC study findings confirm the 3-year overall survival of patients who received durvalumab (IMFINZI) in addition to platinum-based chemoradiation therapy (CCRT) compared to patients who received placebo. The median overall survival (OS) was 13.5 months in the durvalumab group versus 11 months in the placebo group (Hazard Ratio [HR] = 0.69; 95% CI, 0.55-0.86), and the 3-year OS rate was 57% for the durvalumab group compared to 44% for the placebo group (HR = 0.69; 95% CI, 0.55-0.86). This 31% reduction in the risk of death compared to placebo is statistically significant (p < 0.001).

**Patient Selection**

- Patients had to have received at least two cycles of platinum-based chemotherapy concurrently with definitive radiation therapy without progression, and the last radiation dose was 1–42 days before randomization.

**Study Design**

- The PACIFIC study design, eligibility criteria, and assessments have been fully described previously.

**Outcomes**

- Median OS: 13.5 months (IMFINZI) vs. 11 months (placebo) (HR = 0.69; 95% CI, 0.55-0.86)
- 3-year OS rate: 57% (IMFINZI) vs. 44% (placebo) (HR = 0.69; 95% CI, 0.55-0.86)
- 31% reduction in the risk of death compared to placebo (p < 0.001)

**Conclusion**

- The findings from the PACIFIC study demonstrate a significant survival benefit for patients with stage III unresectable NSCLC who received durvalumab plus CCRT compared to placebo, supporting the use of durvalumab as an additional treatment option in this patient population.
Scientific Session I.
Emerging Research Tools in Lung Cancer

Chair: Wan-Seop Kim (Korea)
Tumor-derived EVs have great potential as cancer biomarkers as well as platforms for personalized medicine. Building on the hypothesis that EVs are representative of molecular changes in the tumor, analysis of EVs could form the basis of non-invasive and repeatedly doable molecular testing in body fluid replacing the invasive biopsy technique. This implication of liquid biopsy is clinically relevant in non-small cell lung cancer (NSCLC), especially in EGFR-mutated after the advent of p.T790M mutation targeted agents. In fact, detection of p.T790M mutation by liquid biopsy using plasma cell-free DNA (cfDNA) is recently approved as the companion diagnostics for the 3rd generation EGFR-TKI, osimertinib. At present, liquid biopsy is usually performed by using circulating tumor DNA (ctDNA). Although EGFR mutation testing using ctDNA has been reported to be highly specific, it has the problem of varied sensitivity. The main reason for this high variability in sensitivity when using ctDNA for liquid biopsy lies on the unstable nature of ctDNA in the samples. In contrast, DNA inside a EV is well protected by dual lipid membranous coating and thus has inherent stability. Recently, Thakur BK, et al. have demonstrated that the majority of DNA associated with tumor exosomes are double-stranded in various cancer cell-lines and highlighted the translational value of exosomal DNA for its potential usefulness as a circulating biomarker for cancer detection. On these background, we set up to investigate whether EV DNA might be clinically translated into liquid biopsy for EGFR mutation testing in NSCLC patients. Because plasma samples are known to have limitation of low sensitivity, as mentioned above, we tested the value of bronchoalveolar lavage fluid (BALF) as a liquid biopsy sample, on the basis that BALF derived directly from tumor site is likely to be more efficient than plasma sample from a greater distant site. These finding demonstrate possibility of liquid biopsy using EV DNA potentially replacing the current diagnostic methods for more accurate, cheaper, and faster results.
The search for novel and clinically relevant biomarkers still represents a major clinical challenge and multiplexed omics-based technologies are promising tools to help in this process. Clinical trials are moving toward an array of studies that are more adapted to precision medicine. There is an enhanced need for biomarkers, monitoring devices, and data-analysis methods. Omics profiling using whole genome, epigenome, transcriptome, proteome, metabolome and microscopic histopathology can offer detailed information of the human body in an integrative manner. Omics in addition with pathologic profiles reflect more accurately real-time physiological status.

Personalized omics analyses both disease as a whole and the main disease processes, for a better understanding of the individualized health. Through this, multi-omic approaches for health monitoring, preventative medicine, and personalized treatment can be targeted simultaneously and can lead clinicians to have a comprehensive view on the diseasome. This kind of multiplexed analysis could address both the biology of the tumor and the tumor micro-environment, especially important for predicting cancer responsiveness to immunotherapy. Several technologies aimed at achieving these goals, including multiplex colorimetric immunohistochemistry (mCIHC), multiplex immunofluorescence (mIF), Crispr/cas-amplified multiplexed biomarker, Nanostring, and digital spatial profiling (DSP), and emerging histopathologic biomarkers are discussed.
A subpopulation of non-small-cell lung cancer (NSCLC) is driven by epidermal growth factor receptor (EGFR) activating mutations predicting patient response to tyrosine kinase inhibitors (TKI). Approximately 50–60% of first line TKI treated patients develop therapy resistance due to one common secondary EGFR mutation, T790M. These patients usually, however similarly transient, respond to second line TKI, Osimertinib.

Purpose: Firstly, to determine predictive and prognostic roles of blood-based biomarkers: circulating tumour DNA (ctDNA), circulating tumour cells (CTC) and carcinoembryonic antigen (CEA), in advanced EGFR-mutated lung cancer patients. Secondly, to test the utility of targeted next generation sequencing (NGS) of ctDNA to define putative osimertinib resistance associated mutations.

We analysed 103 serial blood samples from 28 NSCLC patients. ctDNA based EGFR mutation detection by droplet digital PCR (ddPCR) was highly concordant between liquid and tissue biopsy and if detectable at baseline associated with higher disease burden ($p < 0.01$). Early disappearance of ctDNA at 4 weeks was associated with radiological response at 12 weeks of treatment ($p=0.01$) and improved progression free survival (PFS) (HR 5.47, 95%CI 1.32–22.72, $p=0.02$) and overall survival (OS) (HR 5.46, 95%CI 1.28–23.22, $p=0.02$). Similarly, a decrease in CTC counts at 4 weeks was associated with improved PFS (HR 3.81, 95%CI 1.13–12.79, $p=0.03$) but not OS. 85% of patients with radiological progression had a ctDNA rise compared with 22% of patients with stable disease ($p=0.01$). ctDNA rise was seen on average 170 days prior to radiological progression. There was a significant association between
the rise of CEA level with radiological progression (p=0.001).

Studying patients on Osimertinib by NGS showed high concordance to ddPCR for activating EGFR and T790M mutations (R² = 0.92, p < 0.0001). PIK3CA, BRAF and TP53 mutations were found associated with osimertinib resistance.
Education Session I.  
Interventional Bronchoscopy for Cancers

Chair: Choon-Taek Lee (Korea)
Bronchoscopy is a standard procedure in the workup of patients with breathing problems. Another group of tests include spirometries, blood and breath analyses such as capnometry. Some of the disturbances become clinically relevant only when the patient is sleeping. These tests for airflow obstructions are usually performed in sleep labs and not in bronchoscopy suites. A fourth group of investigations includes standardized stress tests, e.g., 6-minute walk or spiro-ergometry. In addition to these physical measurements various imaging techniques are applied. Chest CTs, perfusion and ventilation scans are used to find out, why a patient is short of breath, whether he can undergo surgical resection or whether he would benefit for example from endoscopic lung volume reduction. It is the task of the pulmonologist to put the pieces of the puzzle together in order to establish a diagnosis and guide a therapy.

It is a special challenge to detect and prove disturbances that occur only occasionally and under hardly predictable conditions. A typical example is vocal cord dysfunction. It can mimic asthma but sometimes these patients have completely normal pulmonary function tests when they sit in a body plethysmography box.

We have developed methods to combine diagnostic video-chip bronchoscopy with physiological measurements by attaching sensors and overlay the sensor signals and the endoscopic image. In functional laryngoscopy we have the patient perform tasks such as exercising, while he breathes through a pneumo-tachograph and we observe the laryngeal narrowing with a flexible endoscope. The onset and the degree of laryngeal obstruction and the impaired gas flow are simultaneously displayed and recorded. Inspiratory and expiratory vocal cord dysfunction can be distinguished. In patients with tracheomalacia we observe and measure flow limitation. We can check for example the influence of positive airway pressure or the head position. In patients with tracheal stenoses, we can measure the pressure drop (work of breathing) over the stenotic segment using a double-port catheter that is advanced through the working channel of a bronchoscope. The pressure signals and the airflow are displayed in real time on the screen with the endoscopic image. This helps to determine whether sleeve resection or stent placement are necessary. For emphysema patients endoscopic volume reduction is a potential treatment option. Balloon catheters
with sensitive pressure and flow sensors positioned with bronchosopes are used to measure collateral ventilation or detect air-leaks. For further functional test we attach broncho-suction catheters to gas analysers. Endo-oxymetry and endo-capnometry enable to measure regional oxygen uptake and CO2 clearance of lobes and even segments. In these cases, functional bronchoscopy complements perfusion scans and help to predict for example the functional consequences of lobar resections or valve placements for emphysema patients.

It is relatively simple to combine air flow measurements and gas analyses with flexible bronchoscopy but it can provide very useful information. We are currently developing dedicated systems for functional bronchoscopy that can be applied in clinical practice.
Medical thoracoscopy (MT) is an increasingly common procedure that provides significant clinical information and therapeutic applications. The procedure allows the physician to biopsy the parietal pleura under direct visualization with high accuracy. In addition, one can drain pleural fluid, place a chest tube in a precise location and perform poudrage pleurodesis as a form of recurrence prevention for malignant pleural effusion. MT is carried out in the operating room or procedure suite, under moderate sedation with spontaneous ventilation. In comparison, VATS is performed under general anesthesia, with single lung ventilation and through multiple ports in the operating room.

MT is less invasive, has a comparable diagnostic yield and may be better tolerated in high-risk patients. The indications, complications, and advances in thoracoscopy will be discussed. In the era of rapidly evolving therapeutics for lung cancer, immune-modulation and ever-increasing risks of immunosuppression, MT will evolve and continue to play a pivotal role in the evaluation and research of pleuropulmonary diseases.
Management of Central Airway Obstruction

Hojoong Kim
Division of Pulmonary and Critical Care Medicine, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

Malignant airway obstruction is considered to be one of the most distressing causes of morbidity and mortality in lung cancer patients. Bronchoscopic intervention can provide immediate relief from suffocation, improve general condition, and provide a bridge, allowing time for additional treatment such as surgery, radiation, or chemotherapy in patients suffering from malignant airway obstruction.

Any patients who suffer from respiratory distress due to central airway obstruction are indicated for bronchoscopic intervention. However, patients should tolerate the morbidity of intervention, the length of the airway obstruction less than 4 cm, and the duration of obstruction less than 2 month due to the technical limitation.

Due to it is safe from massive hemoptysis and respiratory failure, most experienced bronchoscopists prefer rigid bronchoscopy under general anesthesia, using intravenous propofol injection. After the induction of anesthesia, the patients are intubated with a rigid bronchoscope tube and a flexible bronchoscope is introduced through the rigid bronchoscope tube, and the narrowed central airway was evaluated. In every case, the obstructed airway is dilated gently using an 10 mm rigid bronchoscope tube initially and then progressively larger bronchoscope tubes until an adequate airway caliber was established. When indicated, a controlled radial expansion balloon is used to enlarge the airway sufficiently to allow bronchoscopic dilatation. Any intraluminal mass is removed mechanically using rigid bronchoscopic forceps or a snare. Frequently, a neodymium-yttrium aluminum garnet (Nd-YAG) or diode laser is used to ablate the residual endobronchial tumor or to cauterize the tumor bed after most of the tumor had been excised. After mechanical dilatation, the airway is maintained by inserting a silicone stent (Dumon-style stent) in patients whose airway is not maintained due to extrinsic compression or malacia. The silicone stents are inserted through the rigid bronchoscope using a standard Dumon technique.

In experienced center, the overall success rate is more than 90% after the emergency bronchoscopic intervention. A successful outcome is accompanied by subjective improvement in the symptoms and radiographic findings. Af-
After stabilizing the airway with the bronchoscopic treatment, favorable outcome is expected if additional definitive therapy can be applied, such as surgery, radiation, or chemotherapy. Nowadays, bronchoscopic intervention can achieve prolonged survival with sustained significant improvement of quality of life.

Bronchoscopic intervention in patients with malignant airway obstruction is helpful for the palliation the airway, allowing the multimodality therapeutic approach and prolonging the life of the patients.
Lung biopsy: How to Overcome the Limitations

Dongil Park
Division of Pulmonary and Critical Care Medicine, Chungnam National University Hospital, Daejeon, Republic of Korea

A lung biopsy is a useful tool in diagnosing various lung diseases, and can be largely divided into a percutaneous/transthoracic approach (transthoracic needle biopsy, TTNB) and endobronchial approaches such as linear EBUS (EBUS-TBNA), radial EBUS (EBUS-GS-TBLB), electromagnetic navigation bronchoscopy (ENB). Image-guided transthoracic needle biopsy (TTNB) is the most commonly used lung biopsy method. Computed tomography (CT) is the most widely used guidance modality, which can be divided into conventional CT (CT), CT-fluoroscopy (CTF), and CBCT (cone-beam CT)-guided TTNB. Ultrasound-guided TTNB is also available for a pleural-based lesion. Diagnostic accuracy and sensitivity for detecting malignancy were 92.1% (9,567/10,383) and 92.1% (7,343/7,975), respectively. In terms of complication, the pooled pneumothorax and hemorrhage rates of CT-guided TTNB were 20.5% and 2.8% respectively. Recently, in order to avoid complications of TTNB, endobronchial approaches have been attempted as much as possible, but there is a limitation in that the accuracy of the examination varies widely depending on the nature and location of the lesion. It is important to select an approach carefully according to the location and nature of the lesion to obtain maximum accuracy while minimizing complications.

References
KASTT Joint Session.
Upcoming Era of Combination Treatment for Advanced EGFR Mutated lung Adenocarcinomas

Chair: Min Ki Lee (Korea)
Tremendous progress has been made in Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) monotherapy as a front line for EGFR mutant non-small cell lung cancer (NSCLC). Previous many trials have shown the superiority of first-line EGFR-TKIs over platinum-based chemotherapy in terms of progression free survival (PFS). Overall survival (OS) is meaningfully improved in recent FLAURA study for osimertinib. The current first line standard of care for patients with advanced EGFR-mutant NSCLC is EGFR-TKI monotherapy. However, the response rate for osimertinib was similar to first generation TKIs in FLAURA. There may be the limitation of EGFR-TKI monotherapy in terms of residual disease. Some preclinical data showed that tumor clones that have the resistance to EGFR-TKIs enhanced the level of vascular endothelial growth factor (VEGF) expression level. For those reasons, combination therapy of EGFR-TKI using chemotherapy and VEGF inhibitor may be essential to meet unmet need.

The combination of chemotherapy and EGFR-TKI is a promising strategy to overcome the residual disease or persist EGFR clones and some studies have shown EGFR mutant NSCLC is more sensitive to chemotherapy compared to wild-type EGFR in terms of response rate. According to NEJ009, which compared the combination of chemotherapy and gefitinib with gefitinib alone, combination therapy meaningfully induces higher overall response rate. Recent studies about combination of chemotherapy and EGFR-TKI have shown the clinical improvement of PFS and OS, but greater toxicities over EGFR-TKI alone.

VEGF inhibitor combined with EGFR TKI improves the delivery of EGFR-TKI to the target sites and has the synergistic inhibition of tumor growth by blocking downstream pathways. According to preclinical data, it is known that VEGF inhibitors like bevacizumab and ramucirumab may delay resistance related to T790M mutation. Recent studies about the combination of VEGF inhibitor and EGFR-TKI have shown the clinical benefit of PFS over EGFR-TKI alone. However, there is a safety concern associated with VEGF inhibitors like proteinuria, hemorrhage, and hypertension. The OS benefit for combination therapy has not been demonstrated yet. According to RELAY study, subgroup analysis of PFS showed the different results compared to previous studies for EGFR-TKI monotherapy. Therefore, target population for combination therapy needs to be defined.
EGFR tyrosine kinase inhibitors (TKI) have shown the efficacy in treatment of lung cancer patients with EGFR sensitizing mutations, and their use has led to a doubling of progression-free survival (PFS) and a lengthening of overall survival (OS) by more than 2 years. However, the emergence of resistance is inevitable, which creates new challenges for the management of patients with EGFR mutant lung cancer. As several approaches after the development of resistance have been suggested, one of them is the continuation of EGFR-TKI with local therapy to aggravated lesions if necessary. This recommendation is based on some studies which showed the survival benefits by the continuation of EGFR-TKI compared with switching to cytotoxic chemotherapy.

Platinum-based chemotherapy (cisplatin or carboplatin) is often used to treat NSCLC, whereas its combination with EGFR-TKI showed mixed results in both pre-clinical studies and in clinical trials. A combination of low-dose Erlotinib and cisplatin may exert a synergistic effect in NSCLC cell lines that contain an EGFR exon 19 deletion, which is probably due to an anti-angiogenesis effect via targeting c-myc/HIF-1α/VEGF signaling. However, a meta-analysis that included 191 randomized phase II trials concluded that the combination of Erlotinib plus carboplatin and paclitaxel did not have a significant beneficial effect on PFS and OS but rather showed more severe adverse effects compared to Erlotinib alone, regardless of the EGFR status.

Pemetrexed has recently been developed to suppress the metabolism of intracellular folic acid, and thus prevent cell division. A combination of Pemetrexed and EGFR-TKI has been highly touted to overcome EGFR-TKI-acquired resistance. The synergistic anti-cancer effect of the combination can only be found in the EGFR-TKI resistant PC9/GR cell line and not in the EGFR-TKI sensitive PC9 cell line, with a possible mechanism of inducing cell apoptosis and suppressing AKT as well as ERK phosphorylation in synergy.
Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) have shown excellent efficacy in patients with EGFR-mutated non-small cell lung cancer (NSCLC). However, acquired resistance inevitably develops after long-term exposure.

Recently, combination therapy has emerged as a promising strategy to delay or overcome acquired resistance to EGFR-TKIs. Many preclinical and clinical studies have been performed to evaluate the efficacy of treatment with EGFR-TKIs combined with other anti-cancer treatments, including cytotoxic chemotherapy, targeted therapy, immunotherapy, and radiotherapy.

This review summarizes preclinical and clinical studies of combination of EGFR-TKIs with non-cytotoxic agent.
A Study on the Combined Treatment of Histone Deacetylase Inhibitor for Improvement of Therapeutic Efficacy of Immune Checkpoint Inhibitors for Lung Cancer

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Immune checkpoint inhibitor (ICI) has been widely applied to various types of cancer therapies and it is used as a treatment in clinical application. However, the treatment efficacy is only about 25%. Therefore, many studies are doing to improve treatment efficiency with co-treatment therapy using chemical medications and ICIs. Histone deacetylase (HDAC) and histone deacetylase inhibitors (HDACi) are attracting attention as factors that can predict the response to treatment with ICIs and increase their efficacy. We conducted experiments by dividing the effects of HDACi on tumor microenvironment into in vitro and in vivo. And we evaluated the clinical implications of HDAC in lung cancer samples through immunohistochemical staining. HDACi showed growth inhibition in mouse lung cancer cell lines (TC-1, LLC) and human lung cancer cell (A549) line compared with normal epithelial cell lines (NIH3T3 and HEK293). Also, we checked ten kinds of immune-related cytokines and chemokines in mRNA level by treated with HDACi. CCL2 and CXCL10 chemokines were significantly increased by dose-dependently. The levels of inflammatory cytokines (interleukin-1β and interleukin-6) were decreased. For in vivo experiment, the combination therapy of HDACi and mouse PD-1 antibody significantly inhibited tumor growth and significantly increased E7-specific IFN-γ-producing CD8+ T cells. In the clinical experiment, total of 92 patients who received ICIs from December 1, 2016 to June 30, 2019 were evaluated. According to the degree of HDAC6 expression, it was divided into a low expression group (n=11) and a high expression group (n=35). The HDAC6 low-expression group revealed high ORR and PFS. In a study on the relationship between the response rate of ICI treatment and HDAC6 expression, the tumor shrinkage rate tended to decrease in inverse proportion to the level of HDAC6 expression. These results indicate that ICI plus HDACi treatment induces tumor growth inhibition through an immune response. HDAC6 expression may predict the prognosis of advanced non-small-cell lung cancer patients treated with ICIs.
Incidence and clinical characteristics of the patients harboring rare mutations other than EGFR or ALK in non-small cell lung cancer: retrospective multicenter cohort study in South Korea

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Background: Several targetable oncogenes such as epidermal growth factor receptor (EGFR) mutation, anaplastic lymphoma kinase (ALK) translocation, ROS1 rearrangement, and BRAF mutation have been identified in the treatment of non-small cell lung cancer (NSCLC) up to date. In particular, it is known that about 60% of patients in lung adenocarcinoma have genetic mutations that can be targeted for the specific targeted agent. The EGFR mutation is found in 40-60%, and ALK translocation is found in 3-7% of lung adenocarcinoma patients. Many studies have shown that tyrosine kinase inhibitors (TKIs), which target EGFR or ALK mutations, have remarkable effectiveness in treating lung adenocarcinoma. Studies are ongoing to apply targeted therapies for the patients who harbor rare genetic mutations and find the novel oncogene that is potential therapeutic targets in NSCLC. However, still no results were reported about diagnostic methods and clinical features of rare and low-frequency genetic mutations of lung adenocarcinoma in Korea.

Methods: In this retrospective cohort study, we will include the patients who were diagnosed or treated with NSCLC from January 2007 to August 2020 at ten tertiary hospitals in Korea. The patients will have a tumor with EGFR/ALK-negative, and positive for any other mutations; RAF, ROS1, c-MET, RET, HER2, FGFR, and NTRK. Approximately 100 patients will be registered, and the data of their demographic factors, stages of lung cancer, diagnostic methods, treatment modalities and results will be collected.

Results: We will analyze and compare the incidence, diagnostic methods, clinical features, and treatment outcomes according to the genetic mutations. We expect patients with rare genetic mutations to have progressive disease, low treatment rates, and poor treatment outcomes because of a lack of treatment modalities.
Satellite Symposium I.
MSD Korea Ltd

Chair: Young-Chul Kim (Korea)
Turn Your Face to Hope for the Patients: Pembrolizumab in the 1st-line Metastatic Squamous NSCLC

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For many decades, platinum-based doublet chemotherapy remained a first line treatment option for patients with advanced squamous NSCLC, which accounts for 25% to 30% of lung cancers. These treatment options had limited efficacy, with a median overall survival of less than 1 year.

The phase 3 KEYNOTE-407 trial enrolled patients with untreated stage IV NSCLC with squamous histology; those with symptomatic brain metastases or pneumonitis requiring systemic steroids were excluded from enrollment. Patients were randomized 1:1 to 200 mg of pembrolizumab plus carboplatin at an area under the curve (AUC) of 6 and either 200 mg/m^2 of paclitaxel every 3 weeks or 100 mg/m^2 of nab-paclitaxel (Abraxane) every week for four 3-week cycles (n = 278), or placebo plus the same schedule of chemotherapy (n = 281). Pembrolizumab and placebo were continued for up to 31 cycles, and patients with progressive disease on placebo were allowed to cross over to pembrolizumab for up to 35 cycles of treatment.\(^1\) Progression-free survival (PFS) per RECIST v1.1, blinded independent central review (BICR) and overall survival served as primary end points of the study. Objective response rate (ORR) and duration of response (DOR) served as secondary end points of the trial. Patients were stratified by PD-L1 expression (tumor proportion score [TPS] <1% vs ≥1%), choice of taxane (paclitaxel vs nab-paclitaxel), and geographic region (east Asia vs rest of the world). In each arm, approximately 35% of patients had less than 1% PD-L1 expression, approximately 40% had 1% to 49% PD-L1 expression, and approximately 25% had 50% or greater PD-L1 expression.

The median OS was 15.9 months with pembrolizumab versus 11.3 months with placebo, meeting the primary end point of the study (HR, 0.64; 95% CI, 0.49-0.85; \(P < .001\)). The hazard ratios for death in the PD-L1–expression subgroups of less than 1%, 1% to 49%, and 50% or greater were 0.61 (95% CI, 0.38-0.98), 0.57 (95% CI, 0.36-0.90), and 0.64 (95% CI, 0.37-1.10), respectively. The median PFS was 6.4 months with pembrolizumab versus 4.8 months with placebo, translating to a 44% reduction in the risk of progression or death (HR, 0.56; 95% CI,
0.45-0.70, \( P < .001 \)). Moreover, the ORR was higher with pembrolizumab, at 57.9\% versus 38.4\% with placebo.

Recently, the efficacy and safety from the phase III IMpower131 study (NCT02367794), which evaluated the combination of atezolizumab and carboplatin-taxane doublet chemotherapy as first-line therapy in patients with stage IV squamous NSCLC, was reported.\(^2\)

As cancer immunotherapy is established as the standard of care in NSCLC, future prospective trials may address the question of whether programmed cell death protein 1 inhibition or PD-L1 inhibition results in favorable treatment outcomes, as cross-trial comparisons are inherently limited owing to the risk of systematic bias and confounding factors.

**Reference**


Oral Presentation I.

Chair: Seung Joon Kim (Korea)
TUMOR SPREAD THROUGH AIR SPACES (STAS): PROGNOSTIC SIGNIFICANCE OF GRADING IN NON-SMALL CELL LUNG CANCER: CAN STAS BE A T FACTOR IN LUNG ADENOCARCINOMA?


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Tumor spread through air spaces (STAS) is an invasive pattern of lung cancer that was recently described. In this study, we investigated the association between the extent of STAS and clinicopathological characteristics and patient outcomes in resected non-small cell lung cancers (NSCLCs).

STAS has been prospectively described from 2008 and graded its extent with a two-tiered system (STAS I: < 2500 μm [one field of x10 objective lens] from the edge of tumor and STAS II: ≥ 2500 μm from the edge of tumor) from 2011 in Seoul National University Bundang Hospital. We retrospectively analyzed the correlations between the extent of STAS and clinicopathologic characteristics and prognostic significance in 1869 resected NSCLCs.

STAS was observed in 765 cases (40.9%) with 456 STAS I (24.4%) and 309 STAS II (16.5%). STAS was more frequently found in patients with adenocarcinoma (ADC) than squamous cell carcinoma, pleural invasion, lymphovascular invasion, and/or higher pathologic stage. In ADC, there were significant differences in recurrence-free survival (RFS), overall survival (OS) and lung cancer-specific survival (LCSS) according to the extent of STAS. In stage IA non-mucinous ADC, multivariate analysis revealed that STAS II was significantly associated with shorter RFS and LCSS (p<0.001 and p=0.006, respectively). In addition, STAS II was an independent poor prognostic factor for recurrence in both limited and radical resection groups (p=0.001 and p=0.023, respectively).

Presence of STAS II was an independent poor prognostic factor in stage IA non-mucinous ADC regardless of the extent of resection.

Keywords: Tumor spread through air spaces, STAS, Adenocarcinoma, Non-small cell lung cancer, Extent of resection, Grading
BALF LIQUID BIOPSY PROVIDES A NOVEL PLATFORM FOR SPEEDY AND ACCURATE EGFR MUTATION TESTING IN ADVANCED NSCLC PATIENTS

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EGFR mutation testing is an essential step for the therapeutic decision in newly diagnosed advanced NSCLC patients and usually performed by using DNA extracted from biopsied tumor tissue with a turnaround time(TAT) of 2-3 weeks. Plasma liquid biopsy using ctDNA is minimally invasive and less time-consuming, but shows limited usefulness due to low sensitivity. We conducted a prospective study to demonstrate clinical usefulness of Broncho-alveolar lavage fluid (BALF) liquid biopsy using extracellular vesicle(EV)-derived DNA in advanced NSCLC patients by comparing the sensitivity and TAT with conventional tissue biopsy and plasma liquid biopsy.

The analysis set for liquid EGFR genotyping is 224 BALF samples and 110 plasma samples obtained from newly diagnosed 224 advanced non-squamous NSCLC patients. EGFR genotyping was done through peptide nucleic acid(PNA)-mediated real-time PCR after extracting BALF EV DNA and plasma cfDNA separately. The sensitivity, specificity, and concordance rate of BALF liquid biopsy were calculated in comparison to matched tissue genotyping and plasma liquid biopsy. In addition, TAT was compared between BALF liquid biopsy and tissue genotyping.

Tissue genotyping revealed 93 EGFR mutant cases(41.5%) and 131 wild-type cases(58.5%). The sensitivity, specificity, positive predictive value, negative predictive value, and concordance rate of BALF liquid biopsy to tissue genotyping were 97.8%, 96.9%, 96.8%, 98.4%, and 97.7%, respectively. BALF liquid biopsy showed almost identical performance with standard tissue genotyping, while only 5 cases were mismatched each other. On the other hand, plasma liquid biopsy using cfDNA(n=110) revealed 48.5% sensitivity, 86.3% specificity, and 63.6% concordance rate in comparison to tissue genotyping. The mean turnaround times of BALF liquid biopsy was significantly shortened to 2.6+2.0 days in contrast to 13.9+12.4 days of tissue genotyping. (p<0.001).

BALF liquid biopsy could be developed as a novel platform for EGFR mutation testing in advanced NSCLC with almost identical performance with conventional tissue genotyping and significantly shortened TAT of 1-2 days.

Keywords: EGFR mutation testing, NSCLC, BALF, Liquid biopsy, Extracellular vesicles
DECONSTRUCTING THE INTRA-TUMOR SUBCLONAL HETEROGENEITY, ALLEL-SPECIFIC HLA LOSS AND IMMUNE ESCAPE OF LUNG SYNCHRONOUS ADENOCARCINOMAS PRESENTING AS GROUND-GLASS NODULES USING WHOLE GENOME SEQUENCING

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Synchronous multiple ground-glass nodules (SM-GGNs) are a unique pathological phenomenon in lung tumors which differ from multiple metastasis lesions but present clinical challenges in surgery setting, therapy decision, and prognosis prediction. One fundamental question is whether SM-GGNs develop from a single malignant clone or from independent progenitor clones.

We sequenced the whole genomes of 30 SM-GGNs and 15 normal controls of the lung tissues to investigate the somatic copy number variations (CNV). Next-generation sequencing was performed using an Illumina mate-pair library protocol. Sequence reads were mapped to the human genome. The cellular subclones were inferred using joint CNV and loss of heterozygosity (LOH) analysis by TITAN program. We presented loss of heterozygosity in human leukocyte antigen (LOHHLA), a computational tool to determine HLA allele-specific copy number from sequencing data.

We found two CNV patterns of SM-GGNs, i.e., strong (parallel) and weak (independent) patterns, which may represent two types of origins. As indicated by the CNV heat-map, primary lung adenocarcinomas and their matched AAHs generated similar global CNV patterns for the parallel pattern. To support this finding, intra-tumor subclonal heterozygosity in SM-GGNs was further examined by comparing the joint CNV and LOH segment landscape. In addition, the cellular subclones shared by parallel lineage SM-GGNs had more genomic features with higher prevalence compared to SM-GGNs with independent lineage. We using LOHHLA, we find that HLA LOH occurs in 17.39% of SM-GGNs and is associated with a high subclonal neoantigen burden.

These findings provide insight into biology of SM-GGNs, which in turn will help pathological staging of SM-GGNs and therefore guide the treatment decisions.
Keywords: Lung cancer, Ground-glass Nodule, HLA LOH, Subclone
MMP1/9/10/11/15 AS POTENTIAL TARGETS AND MMP12/13/14/28 AS NEW BIOMARKERS FOR THE PROGNOSIS OF HUMAN LUNG CANCER

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Matrix metalloproteinases (MMPs) are a group of zinc-dependent endopeptidases involved in extracellular matrix (ECM) degradation and remodelling which are supposed to play pivotal roles in a variety of cancer types during the procedure of local invasion and distant metastasis. In total, 23 MMPs are recognised in human beings and usually categorized as collagenases, stromelysins, gelatinases, membrane-type or other miscellaneous type based on substrate specificity. The aberrant expression of MMPs and their association with clinicopathologic parameters and prognosis in NSCLC had not been fully elicited.

In the present study, using Oncomine gene expression array database (http://www.oncomine.org), Gene Expression Profiling Interactive Analysis (GEPIA), Kaplan Meier-plotter (http://kmplot.com), TCGA data/ cBioPortal analysis and Gene oncology/pathway enrichment analysis we found that MMP1/9/10/11/12 were enhancedly expressed in both squamous cell carcinoma (SCC) and adeno-carcinoma (ADE) histologies, while enhanced expression of MMP2/14 and altered expression of MMP7/13/15/28 were merely determined in SCC and ADE tissue, respectively (Figure 1). Expression of MMP9/11/14 was positively and expression of MMP15 was negatively correlated with advanced staging in both histologies of NSCLC respectively, while further analyses demonstrating the positive correlation of MMP10/14 and SSC staging as well as that of MMP1/14 and ADE staging. Survival analyses revealed that MMP9/11/12/14 were impairing factors while MMP15/28 were protecting factors for overall survival (OS) in NSCLC patients. Enhanced expression of MMP9/11/12/13/14 correlated with shorter time interval from surgical resection to first progression (FP) while enhanced MMP28 expression correlated with longer progression-free survival. KEGG pathway enrichment indicated pivotal role of MMP1/2/9 in bladder cancer (12.96%, P=0.001), MMP3/9/14 in TNF signaling pathway (12.96%, P=0.004) and MMP1/2/9 in pathways in cancers (12.96%, P=0.043).

MMP1/9/10/11/15 as potential targets and MMP12/13/14/28 as new biomarkers for the prognosis of human
Keywords: Matrix metalloproteinase, Non-small cell lung cancer, Prognosis
EGFR ANALYSIS OF MULTIPLE LUNG CANCER: CLINICOPATHOLOGIC REVIEW

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Lung cancer is one of the leading causes of death worldwide and primary lung cancer that occurs multifocally is reported to account for 0.2~8.1%. As tyrosine kinase inhibitor targeting EGFR has been widely used, EGFR analysis of non-small cell lung cancer is one of the essential process of treatment of non-small cell lung cancer. However, the effectiveness of EGFR analysis in all of tumors in multifocal lung cancer has been questioned because sufficient research has not been conducted on whether different tumors of the same patient show different EGFR profiles. The aim of this study is to evaluate the results of EGFR analysis of multifocal lung cancer and to find out the concordance of EGFR clonality in multifocal lung cancer.

All patients who underwent surgery with lung cancer from 2017 to 2020 at the Samsung Medical Center were enrolled. We reviewed the results of patients with multiple lung cancers who performed EGFR analysis. For the EGFR analysis, Cobas® EGFR mutation test v2 was used.

The results of EGFR analysis from 101 patients with multifocal primary lung cancer were reviewed. Our study revealed that 51 patients (50.5%) had different EGFR mutations. There was no clinicopathologic parameters significantly associated with concordance of EGFR mutation between multifocal lung cancers.

It is well worth considering the possibility of different EGFR mutations in the multifocal lung cancers, unless when it is highly predicted to show the same clonality, such as the intrapulmonary metastasis.

Keywords: Lung Cancer, EGFR, Synchronous Multifocal Neoplasm, Lung cancer
Immunotherapy has improved the overall survival of lung cancer patients, but some patients have a hyperprogression of their tumor as a result. It is defined as hyperprogressive disease (HPD). However, there is still no consensus on how to evaluate this novel pattern of progression. The aim of this study was to introduce the characteristics of HPD and investigate its predictive markers by semiautomatic software package.

We investigated patients with recurrent and/or metastatic NSCLC treated with PD-1/PD-L1 inhibitors between January 2015 and August 2019. Radiological images were quantitatively and longitudinally evaluated for tumor volume and diameter by comparing baseline and follow-up computerized tomography images. The primary endpoint was effect on overall survival (OS) of HPD in patients treated with immunotherapy using both method Semiautomatic software (syngo.via MM Oncology Clinical Applications, Oncology, Siemens® Medical Solutions, Molecular Imaging, Hoffman Estates, IL USA Inc.) and RECIST.

A total of 219 patients treated with PD-1/PD-L1 inhibitors (169, 77.2% male), 71.2% (n = 156) were 60 years or older, 65.7%(n = 142) had nonsquamous histology, and 83.1% (n = 182) received a one or two previous lines of chemotherapy. The median overall survival (OS) was 18.4 months (95% CI, 12.1-24.7 months). HPD was observed in 35 (15.9%) and 39 (17.8%) patients according to Semiautomatic software volumetry (HPDV) and assessed by the Response Evaluation Criteria in Solid Tumors version 1.1 criteria (HPDR). HPDV group had lower post-immunotherapy OS (median of 2.67 months; 95% CI, 0.42-4.90) when compared with the non-HPD PD group (median, 5.40 months; 95% CI, 4.25-6.54; P-value 0.105). HPDR group had also lower post-immunotherapy OS (median of 4.33 months; 95% CI, 2.12-6.54) when compared with the non-HPD PD group (median, 5.47 months; 95% CI,
Semiautomatic analyses of HPD in lung cancer is feasible. It is more accurate than standard RECIST method. In a multivariate analysis, low PD-L1 expression, high neutrophil-to-leukocyte ratio, more than 3 metastatic sites and low hemoglobin were independent predicting factor for HPD.

Keywords: Lung cancer, Immune checkpoint inhibitor, Hyperprogression, Volumetry

Table 1. Factors Associated with HPD as Determined by Univariate and Multivariate Analysis

<table>
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<th>Parameters</th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>P-value</th>
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<td><strong>Univariate</strong></td>
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<tr>
<td>PD-L1 &gt;=50% vs &lt;50%</td>
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<td>1.761-9.314</td>
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<tr>
<td>Previous lines of treatment &lt;3 vs &gt;=3</td>
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<td>1.005-5.384</td>
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<td>1.305-5.820</td>
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<td>PLR &lt;214 vs &gt;=214</td>
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<td>1.053-4.545</td>
<td>0.036</td>
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<tr>
<td>Hb &gt;=10 vs &lt;10</td>
<td>4.501</td>
<td>2.075-9.763</td>
<td>&lt;0.001</td>
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<tr>
<td>Alb &gt;=3.5 vs &lt;3.5</td>
<td>2.668</td>
<td>1.220-5.835</td>
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<td><strong>Multivariate</strong></td>
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<td>PD-L1 &gt;=50% vs &lt;50%</td>
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<td>1.684-9.081</td>
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COMPARISON OF EPIDERMAL GROWTH FACTOR RECEPTOR TYROSINE KINASE INHIBITORS FOR PATIENTS WITH LUNG ADENOCARCINOMA HARBORING DIFFERENT EPIDERMAL GROWTH FACTOR RECEPTOR MUTATION TYPES

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Epidermal growth factor receptor (EGFR) mutations in non–small-cell lung cancer predict sensitivity to EGFR tyrosine kinase inhibitors (TKIs). EGFR mutation types are associated with efficacy of EGFR TKIs. We investigated the clinical outcomes of afatinib, erlotinib, and gefitinib according to EGFR mutation type in patients with lung adenocarcinoma.

Between May 2010 and December 2018, we investigated 363 patients with advanced lung adenocarcinoma harboring EGFR mutations who received EGFR TKIs. Efficacies of EGFR TKIs such as response rate, progression-free survival (PFS), and overall survival (OS) were retrospectively evaluated according to exon 19 deletion (E19del), L858R point mutation (L858R) and uncommon mutations.

The frequency of E19del was 48.2%, that of L858R was 42.4%, and that of uncommon mutations was 9.4%. E19del and L858R were associated with superior PFS and OS compared with uncommon mutations. Erlotinib showed significantly inferior OS than other TKIs (30.8 ± 3.3 in erlotinib vs. 39.1 ± 4.3 in afatinib vs. 48.4 ± 6.3 in gefitinib; p = 0.031) in patients with L858R. Gefitinib showed significantly inferior PFS (4.6 ± 1.1 in gefitinib vs. 11.6 ± 2.7 in afatinib vs. 10.6 ± 2.7 in erlotinib; p = 0.049) in patients with uncommon mutations.

Afatinib was significantly associated with a longer PFS, presenting constant effectiveness in all EGFR mutation types. Caution may be needed on the use of erlotinib for L858R and the use of gefitinib for uncommon EGFR mutations.

Keywords: Epidermal growth factor receptor, Non-small cell lung cancer, Adenocarcinoma, Survival, Tyrosine kinase inhibitor
THE IMPACT OF PROGRAMMED DEATH-LIGAND 1 EXPRESSION ON THE PROGNOSIS OF EARLY-STAGE RESECTED NON-SMALL CELL LUNG CANCER: A META-ANALYSIS OF LITERATURES

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Previous studies have demonstrated that programmed cell death-ligand 1 (PD-L1) serves as biomarker for poor prognosis and survival in advanced-stage non-small-cell lung cancer (NSCLC) patients. However, the merit of PD-L1 expression to predict the prognosis of early-stage NSCLC patients who underwent complete resection remains controversial. In the present study, we performed a meta-analysis to investigate the relationship between PD-L1 expression and prognosis in patients with early-stage resected NSCLC.

Electronic databases, including PubMed, EMBASE, and the Cochrane Library, were searched until July 23, 2020, for studies evaluating the expression of PD-L1 and the prognosis of resected NSCLCs. Hazard ratios (HRs) with 95% confidence intervals (CI) of overall survival (OS) and disease-free survival (DFS) were pooled and analysed. Heterogeneity and publication bias analyses were also assessed.

A total of 15 studies involving 3790 patients were considered in the present meta-analysis. The pooled HR indicated that PD-L1 expression related to a much shorter DFS (HR = 1.56, 95% CI: 1.18-2.05, p<0.01), as well as a significantly worse OS (HR = 1.68, 95% CI: 1.29-2.18, p<0.01). Furthermore, our analysis indicated that PD-L1 expression was significantly associated with gender (male vs. female: OR = 1.27, 95% CI: 1.01-1.59, p=0.038), histology (ADC vs. SCC: OR = 0.54, 95% CI: 0.38-0.77, p=0.001), TNM stage (I vs. II-III: OR = 0.45, 95% CI: 0.34-0.60, p=0.000), smoking status (Yes vs No: OR = 1.43, 95% CI: 1.14-1.80, p=0.002) and lymph node metastasis (N+ vs N−: OR = 1.97, 95% CI: 1.26-3.08, p=0.003).

The results of this meta-analysis suggest that PD-L1 expression predicts an unfavourable prognosis in early-stage resected NSCLCs. The role of personalized anti-PD-L1/PD-1 immunotherapy in the adjuvant settings of resected
NSCLC warrants further investigation.

**Keywords:** PD-L1, NSCLC, Meta-analysis, Prognosis, Resection
CIRCULATING TUMOR CELLS AND PERIPHERAL BLOOD CELLS AS PREDICTIVE MARKERS FOR IMMUNOTHERAPY IN ADVANCED NON-SMALL CELL LUNG CANCER

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This study aimed to investigate the feasibility of circulating tumor cells (CTCs) and peripheral blood cells (PBCs) as predictive markers for immunotherapy in advanced non-small cell lung cancer (NSCLC).

This study included patients with advanced NSCLC receiving pembrolizumab or atezolizumab from July 2019 to June 2020. Blood was collected in K2-EDTA tube before each administration from cycle 1 to 4 (C1-4), and PBC counts (absolute neutrophil count[ANC], neutrophil-to-lymphocyte ratio[NLR], derived NLR[dNLR], platelet-to-lymphocyte ratio[PLR]) were calculated at each cycle. CTCs were enriched by using CD-PRIMETM system, the antibody-independent size-based isolation method, and identified by single positive cells (EpCAM/CK+CD45-) in Bioview CCBS system.

Among 83 response-evaluable patients, objective response rate was 21% and durable clinical benefit (DCB) were 35%. Baseline (C1) CTC and PBC count did not show a significant difference according to best response and DCB. However, patients with lower NLR, dNLR and PLR at C1 showed significant benefit in progression-free survival (PFS) and overall survival (OS) (p<0.05 for all). Patients with decreased CTC at C2 compared to C1 showed benefit in median PFS (6.2 vs 2.3, p=0.078) and OS (not reached [NR] vs 6.8, p=0.021) than those with increased CTC count. Patients with decreased ANC and NLR at C3 compared to C1 showed benefit in median PFS (6.3 vs 1.9, p=0.001 and 6.3 vs 1.9, p=0.007) and OS (NR vs 5.1, p=0.014; NR vs 6.8, p=0.045) than those with increased ANC and NLR. Low dNLR (≤2.0) and PLR (≤210) at C1, and decreased CTC at C2 compared to C1 were the independently significant factors for survival (Fig. 1).

The CTC and PBC count at baseline and their changes during treatment could be potential biomarkers to predict the survival benefit and may help risk-group stratification in patients with advanced NSCLC who received anti-PD-1/PD-L1 immunotherapy.
Keywords: Circulating tumor cell, Peripheral blood cell, Biomarker, Programmed cell death protein 1, Non-small cell lung cancer
FUNCTIONAL ROLE OF COMPOUND EGFR MUTATION AND ITS POTENTIAL PREDICTIVE VALUE ON ARCHIVAL TUMOR TISSUES OF THE LUNG ADENOCARCINOMA PATIENTS HARBORING EGFR MUTATIONS.

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Treatment strategies for non-small cell lung cancer are rapidly developing, and various schemes are being studied to achieve the best results with the best combination and sequence of various modalities. In particular, since the prevalence of up to 35-40% EGFR mutation harboring lung adenocarcinoma in East Asia is higher than that of western 15-17%, studies related to the oncogenic addiction are being conducted. Recently, post hoc analysis of LUX-lung study and clinical study of compound mutation through KCSG-LU15-09 clinical study are published, and adjuvant EGFR TKI after surgical resection of lung adenocarcinoma through SELECT trial and ADJUVANT study. The efficacy of based on these studies, compound EGFR mutations affect morphological changes and protein expression signaling systems, leading to early recurrence and poor prognosis after surgery. So new treatment strategies need to be established. This study was aimed to prove through clinical data and in vitro experiments that when compound EGFR mutations are identified through the nucleotide sequence analysis of Exon 18-21, different proteins are expressed according to their type, number, and combination, and the signaling system changes.

We evaluated EGFR mutation status by performing PNA clamping, ddPCR and Next generation sequencing (NGS) quantitative data analysis of 802 patients with EGFR + after surgery at the Department of Thoracic Surgery at Seoul St. Mary’s Hospital from 2010 to 2018.

Among the 802 cases confirmed to be EGFR positive in the surgical specimen, 713 cases that can be analyzed were examined in detail. For 150 cases, NGS was performed after lung resection, 419 cases were PNA clamp ddPCR after lung resection, and PNA clamp ddPCR after metastatic site op for 144 cases. Common mutation was 652 (91.46 %), major uncommon mutation was 18 (2.52 %), Exon 20 insertion was 17 (2.38 %), minor uncommon mutation was...
8 (1.12 %), and compound mutation was 18 (2.52 %). Interestingly, compound mutations or uncommon mutations did not appear to affect survival in particular (p=0.95, 0.48).

When the conformation of the EGFR kinase domain was considered, it was confirmed that compound mutation occurred at the approximate location in the molecular configuration. PNA clamps are conveniently detecting the EGFR mutation with excellent yield, but since they are designed to detect only known hot spots, further analysis for NGS sequencing is in progress. Research is underway to read the E18–21 sequence by sanger sequencing and identify all known uncommon mutations and unknown uncommon mutations.

Keywords: Non-small cell lung cancer, EGFR mutation, Compound mutation
Education Session II.
SCLC and Other Thoracic Malignancies

Chair: Sung Yong Lee (Korea)
Incorporation of Immuno-oncology in SCLC

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Some immune checkpoint inhibitors (ICIs) have been approved for the treatment of small cell lung cancer (SCLC). Here I summarize the results of clinical trials which were the basis of the approval of these drugs and discuss the limitations of benefit from these drugs and future direction of immuno-oncology in SCLC.

Nivolumab and pembrolizumab have been approved as salvage treatment for SCLC after standard of care. Both drugs are accelerated approval based on tumor response rate and durability of response.

Nivolumab was approved by US FDA for metastatic SCLC whose cancer has progressed after platinum-based chemotherapy and at least one other line of therapy. The approval was based on the result of CheckMate-032 SCLC cohort. The objective response rate (ORR) was 12% (13/109, 95% CI: 6.5-19.5) in patients who experienced disease progression after platinum-based chemotherapy and at least one other line of therapy. The median duration of response (DOR) was 17.9 months (95% CI: 7.9-42.1 months, range: 3.0-42.1 months).

Pembrolizumab had the same indication with that of nivolumab, meaning the third line treatment in patients who experienced disease progression after platinum-based chemotherapy and at least one other line of therapy. The approval was based on pooled data from KEYNOTE-158 and KEYNOTE-028. The ORR was 19% (16/83, 95% CI: 11-29) and 56% of them had a DOR of 18 months or longer (range: 4.1-35.8+ months).

Atezolizumab and durvalumab can be used as first-line treatment combined with standard of care, etoposide and platinum in extensive stage SCLC.

Atezolizumab combined with etoposide and carboplatin 4 cycles, followed by atezolizumab maintenance could be used as a standard of care now. The phase 3 trial showed that the median OS was improved for the atezolizumab versus placebo group. It was 12.3 versus 10.3 months (hazard ratio [HR]: 0.70, 95% CI: 0.54-0.91). Median PFS was also improved among those receiving atezolizumab, showing 5.2 versus 4.3 months (HR: 0.77, 95% CI: 0.62-0.96).
Durvalumab also improved OS when combined with etoposide and platinum (~1/3 cisplatin or ~2/3 carboplatin) and used as maintenance. The median OS was 12.9 versus 10.5 months (HR: 0.75, 95% CI: 0.62-0.9). PFS was not formally tested for significance, but HR was reported 0.80 (95% CI: 0.66-0.96).

Despite of recent advances in IO for SCLC treatment, the amount of benefit is not satisfactory. The limitations of IO in SCLC could be from harsh immune microenvironment such as down regulation of MHC class I, low expression of PD-L1, poor infiltration of effector T-cells and presence of myeloid-derived suppressor cells and regulatory T-cells. The way to improve the efficacy of IO for SCLC could be the combination of ICI other than PD-(L)1 inhibitor, suggesting from the data of nivolumab and ipilimumab combination therapy.
Small-cell lung cancer (SCLC) is a high-grade neuroendocrine tumor characterized by rapid growth, early metastasis, and acquired therapeutic resistance, and limited progress has been made in the treatment of this disease over the past three decades.

The previous studies confirmed the nearly universal functional loss of the two key tumor suppressor genes, TP53 and RB1, in SCLC. Disappointingly, recurrent targetable mutations in known oncogenes, such as those seen in the kinases that comprise targetable drivers in lung adenocarcinoma, were found to be rare in SCLC.

By contrast, frequent copy number amplification of MYC family proto-oncogenes was observed, consistent with prior studies in cell lines and genetically engineered mouse models implicating this gene family in SCLC carcinogenesis.

Recently, several lines of evidence, from SCLC primary human tumors, patient-derived xenografts, cancer cell lines and genetically engineered mouse models, showed to be converging on a new model of SCLC subtypes defined by differential expression of four key transcription regulators: achaete-scute homologue 1 (ASCL1, also known as ASH1), neurogenic differentiation factor 1 (NeuroD1), yes-associated protein 1 (YAP1) and POU class 2 homeobox 3 (POU2F3).

Nonetheless, advances in our understanding of multiple aspects of the biology of SCLC have led to the development of new therapies that are currently under clinical investigation.

Some novel treatments such as lurbinectedin, novel immune-targeted approaches against surface markers such as DLL3, and combination strategies of DNA-damage response inhibitors with immunotherapy may provide a broader therapeutic opportunity in SCLC patients.

However, we must foster further research and prospective studies to identify valuable, predictive biomarkers to determine those individuals who might benefit from therapeutic intervention, and to meaningfully improve clinical outcomes for patients with SCLC.

In this lecture, novel therapeutic approach will be discussed based on molecular subtypes, biomarker, mechanism of tumorigenesis in SCLC.
Recent Update in Thymic Malignancy Treatment

Se-Hyun Kim
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Thymic malignancies are rare mediastinal cancers, which include thymoma and thymic carcinoma. Treatment guidelines for these rare tumors are primarily based on small prospective studies and retrospective study of a national database and recommend the multi-disciplinary team approach of thoracic surgeons, radiation oncologists, and medical oncologists to decide the treatment plan. In resectable or potentially resectable thymic malignancies, adjuvant or neoadjuvant chemotherapy with cytotoxic agents can be considered to reduce tumor recurrence after surgery or increase resectability. In metastatic or recurrent thymic malignancies, cytotoxic chemotherapy can be regarded as a treatment option for symptom palliation. In patients who failed to platinum-based chemotherapy, novel therapeutic agents such as small molecule tyrosine kinase inhibitors and immune checkpoint inhibitors are investigated in recent clinical trials. Further clinical investigations of thymic malignancies to develop effective systemic treatments are warranted.
Malignant pleural mesothelioma (MPM) is a rare but highly aggressive thoracic malignancy, typically associated with previous asbestos exposure, which accounts for 80% of all cases. Most of MPM cases are unresectable when initially found, and a grave clinical outcome is well known with <10% of 5-year overall survival (OS) rate. Meanwhile, its incidence has risen steadily in the last decade due to a long latency time up to 30~50 years, and is expected to have its peak in the next decade. Considering its increasing incidence and fatality, there is a clear unmet need in therapeutic strategy of MPM.

Due to its rarity and histologic heterogeneity, there has long been great challenges of therapeutic progress in MPM, mainly due to the relative lack of organized randomized clinical trials and biologic understanding for the disease. However, with several landmark trials, cisplatin plus pemetrexed doublet chemotherapy constitutes current standard frontline treatment for most of unresectable, advanced MPM. Unfortunately, pemetrexed-based 1L chemotherapy still seems suboptimal with median OS of approximately 12 months, and the benefit of pemetrexed maintenance remains yet unclear. Moreover, there has been no established later line treatment options except a few modest single chemotherapeutic regimen (e.g. vinorelbine, gemcitabine). These all indicate an urgent need for developing novel systemic therapeutic options in advanced MPM. Based on the recent advance in sequencing technologies and biologic understanding of MPM, there has been increasing attempts for discovery of novel targeted therapies and immunotherapies. Immune-checkpoint inhibitors (ICIs) are also abundantly investigated in advanced MPM. Earlier studies with ICIs monotherapy in later-line failed to show a significant survival benefit, and current efforts have been focused on combination strategies, particularly in front-line setting. Recently, CM-743 has been the first positive randomized phase III trial that proved a significant OS benefit of nivolumab plus ipilimumab combination in 1L treatment compared with standard chemotherapy. As for targeted treatment, some anti-angiogenic agents as Bevacizumab showed a substantial promise in efficacy outcomes when added to cisplatin and pemetrexed, but its magnitude of benefit seems still insufficient to be highly endorsed. Other targets of interest include...
PI3K, PARP, HDAC, FAK, BAP1 and EZH2, and targeting mesothelin is also under investigation. However, response to these targeted therapies has been mostly hampered and disappointing, which suggests an existence of intra-tumoral heterogeneity and also an uncertainty of 'driver-ness' of these actionable mutations.

In this lecture, we will review more in detail the current standard and upcoming systemic treatment options for MPM, specifically focusing on unresectable, advanced MPM. Moreover, we will share several unsolved issues for the treatment of MPM and discuss our future directions.

**Figure.** Potential molecular targets of MPM and related novel therapeutics
Education Session III.
Treatment of N2-Positive Lung Cancer

Chair: Deog Gon Cho (Korea)
Updates on the Mediastinal Staging

Bin Hwangbo
Department of Pulmonology, National Cancer Center, Goyang, Korea

Mediastinal lymph node (LN) staging is an important step to guide treatment decision in non-small cell lung cancer (NSCLC). The first step of clinical nodal (cN) staging is the imaging study. However, the sensitivity of CT and PET scans for identifying mediastinal metastasis were approximately 55% and 77% respectively by a meta-analysis. To overcome the limitations of imaging studies, invasive mediastinal staging which obtain cyto-pathological specimens from LNs is recommended. Cervical mediastinoscopy was the gold standard of invasive cN staging. Currently, minimally invasive methods, such as endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA), have widely replaced the role of cervical mediastinoscopy. According to the meta-analysis by the American College of Chest Physicians in 2013, the pooled sensitivity of EBUS-TBNA in LN staging was 89% which was similar with that of video assisted mediastinoscopy. Endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) which targets mediastinal LNs though the esophagus is another endoscopic staging method. Endoscopic ultrasound-with bronchoscope guided fine needle aspiration (EUS-B-FNA) that uses an ultrasound bronchoscope for transesophageal approach is an alternative to conventional EUS-FNA. Because EBUS-TBNA and EUS-(B)-FNA have different accessibility to the mediastinum, combined EBUS/EUS staging in lung cancer has been studied. After proper staging with EBUS-TBNA, the additional gain in sensitivity of the combined EBUS/EUS-B approach was 5-7%. The indications to add EUS-(B) following EBUS-TBNA have not been determined. However, EUS-B-FNA can be considered when we encounter LNs accessible only by EUS-B-FNA and the status of LNs can affect treatment decision. Although endoscopic staging methods are less invasive than mediastinoscopy, serious complications such as mediastinitis can occur. Knowledge on the risk of complications and careful procedures are needed.
Role of Surgery in N2 Diseases

Takahiro Nakajima
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Patients with non-small-cell lung cancer with mediastinal nodal metastasis (N2 disease) are a heterogeneous population treated by upfront surgery, neoadjuvant therapy followed by surgery, definitive chemoradiotherapy, and best supportive care. With recent advances in systemic chemotherapy, such as the advent of molecular-targeted therapies and immunocheckpoint inhibitors, the significance of local treatment has increased.

Surgery alone is not recommended for N2 disease, and multimodal treatment should be considered. Surgical intervention should be decided based on the preoperative accurate nodal staging. An endoscopic ultrasound-guided needle biopsy is recommended as the first test. Surgeons should then evaluate the resectability of the disease based on computed tomography findings. Complete resection while avoiding pneumonectomy is important when selecting candidates for multimodal treatment, including radical surgery. Vascular- as well as broncho-plastic procedures are often warranted the preservation of the lung parenchyma.

The efficacy of neoadjuvant therapy is still controversial, and promising results from the latest clinical trials including molecular-targeted therapy and immunocheckpoint inhibitors are expected. Patients found to have mediastinal nodal metastasis postoperatively require adjuvant therapy. Previous studies have shown a 5%-10% survival benefit by systemic adjuvant chemotherapy, however, there has been little progress over the past decade regarding the development of cytotoxic chemotherapeutic agents. New endeavors concerning adjuvant therapy with targeted therapeutic agents or immunocheckpoint inhibitors are also expected.

Surgeons should therefore compare the outcomes associated with different types of definitive chemoradiotherapy when considering the surgical indication for N2 disease. Recent advances with regard to the combination of chemoradiotherapy followed by immunocheckpoint inhibitor has resulted in an improved prognosis for N2/3 patients. Multimodal treatment including surgery is therefore expected to have a clinical outcome with a more than 60% overall survival in the future.
Surgeons always treat patients with the goal of achieving a “cure” for the disease. Thus far, we have selected candidates with N2 disease expected to have the best outcome following multimodal treatment, including surgery, based on our sense, in what we call the “art” of surgery. However, advances in precision diagnostic technology will enable the stratification of patients for optimal treatment planning. The development of systemic therapeutic agents is fast, and the results of clinical trials have demonstrated the effectiveness of immunocheckpoint inhibitors without elucidating the mechanisms of such drug effectiveness. In the precision oncology era, surgeons should apply basic principles flexibly to individual patients. Artificial intelligence technology may also help surgeons hone their “art” in the near future.
Immunotheapy and targeted therapy have dramatically changed the treatment landscape of non-small cell lung cancer (NSCLC). Nowadays, these drugs are being studied in the neoadjuvant and adjuvant setting to reduce the systemic recurrence and improve survival. ADAURA trial showed the marked disease-free survival benefit with osimertinib over placebo in surgically resected NSCLC population. Incorporating these very potent and CNS-penetrating drug into the neoadjuvant setting may have great impact on the survival of patients with potentially resectable NSCLC. Ongoing large neoadjuvant trials of immunotherapies and molecular therapies alone and in combination with chemotherapy are underway and eagerly awaited.

Reference

Role of Postoperative Radiotherapy in Resected N2 Disease

Byoung Hyuck Kim
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There has been a constant debate regarding the appropriate use of postoperative radiotherapy (PORT) for patients with completely resected N2 NSCLC. Since the publication of PORT meta-analysis in 1998, there was a sustained decline in PORT use for N2 NSCLC during the past 20 years. However, previous PORT meta-analysis has some drawbacks in that most trials included in this study were associated with obsolete radiotherapy and inadequate staging. After that, many practical changes happened including better patient selection, adopting adjuvant chemotherapy, and better surgery/radiotherapy techniques. Recent retrospective studies, meta-analysis, or large database analysis seem to favor PORT. Especially, significant survival benefit from PORT were observed in patients with adverse factors such as multi-N2 stational nodal disease, high lymph node ratio, extracapsular extension, or squamous cell carcinoma. However, no robust data still exists. The first randomized controlled trial using three-dimensional conformal RT was reported in 2014 comparing adjuvant chemotherapy vs. adjuvant CCRT in N2 NSCLC. In result, adjuvant CCRT significantly increased DFS and improved OS in patients with 2 or more N2 nodes. Recently at ESMO20, LungART trial which is the 2nd randomized study evaluating modern PORT after complete resection, finally out. Mediastinal relapse was reduced by PORT (46% vs. 25%), but it did not translate into DFS benefit (3 year 43.8% in the control vs. 47.1% in the PORT arm, HR 0.85, p = 0.16). More cardiopulmonary toxicities were observed that need to be further explored. In conclusion, routine PORT for all resected N2 NSCLC is no longer standard of care but other individualized approaches are required. Evolving neoadjuvant or adjuvant chemotherapy combined with immunotherapy could change PORT indications. IMRT or proton beam RT may reduce toxicities and improve the therapeutic ratio.
Oral Presentation II.

Chair: Sei-Hoon, Yang (Korea)
CT MEAN DENSITY IS ASSOCIATED WITH PATHOLOGICAL INVASION FOR PURE GROUND-GLASS NODULES

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Objective: With the widely applied of low-dose thin section CT, more and more Pure ground-glass nodules (pGGNs) are found in CT scanning screening. Although most pGGNs on CT are regarded as adenocarcinoma in situ (AIS) and minimally invasive adenocarcinoma (MIA), a part of pGGNs is confirmed to be invasive adenocarcinoma (IAC) pathologically. The purpose of this study was to find clinical and radiological indicators that distinguish IAC from AIS/MIA.

Methods: From January 1, 2014 to October 31, 2019, patients with completely resected adenocarcinoma appearing as pGGNs within 3cm in CT scan were reviewed. The relationship between clinical and radiological information and pathological invasion of pGGNs was evaluated by univariate and multivariate analyses.

Results: A total of 919 patients were included in this study. Among the 919 patients, 183 (19.9%) were AIS, 549 (59.7%) were MIA, and 187 (20.3%) were IAC. In univariate analysis, there were significant difference between the two groups among sex (P=0.004), age (P<0.001), smoking habits (P=0.018), maximum diameter (P<0.001), mean density (P=0.001), volume (P<0.001), lobulation sign (P<0.001), spiculation sign (P<0.001), roundness (P=0.003), variance (P<0.001), skewness (P<0.001), kurtosis (P<0.001), entropy (P<0.001). Logistic regression analysis demonstrated that age (OR: 1.041, 95%CI: 1.023-1.060, P <0.001), maximum diameter (OR: 1.167, 95%CI: 1.123-1.213, P <0.001), and mean density (OR: 1.003, 95%CI: 1.001-1.006, P =0.005) were clinical and radiological factors associated to IAC. The model between those three factors and IAC with an area under curve (AUC) of 0.737 in ROC curve.

Conclusions: Age, maximum diameter and mean density are independent risk factors for predicting IAC in patients with pGGNs. Indexes related to CT density histogram have no obvious advantages in distinguishing pathological types of pGGNs.

Keywords: Pure ground-glass opacity, Lung adenocarcinoma, CT mean density
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DEVELOPMENT AND VALIDATION OF MACHINE LEARNING-BASED MODEL FOR THE PREDICTION OF MALIGNANCY IN MULTIPLE PULMONARY NODULES: ANALYSIS FROM MULTICENTRIC COHORTS

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With the wide-spread use of thoracic computed tomography (CT) scan, the incidence of multiple pulmonary nodules (MPNs) has increased dramatically in recent years, imposing significant pressures on nodule evaluation. However, no tool has been established to help in this process, leading to the confusion in the choice of optimal management by clinicians. This study aimed to develop and validate a machine learning-based model to estimate the probability of malignancy especially for MPNs to guide decision-making.

From 2007 to 2018, 520 consecutive patients with newly discovered MPNs in a Chinese center were reviewed. A total of 1739 nodules (including 876 malignant nodules) discovered on CT scans were labeled and included in the development cohort. Several machine learning algorithms were compared on this cohort without hyperparameter optimization, and finally XGBoost algorithm performed the best thus was selected to develop the model (PKU-M model) by utilizing clinical-radiological features. Grid search and 10-fold cross-validation were performed to select and fine-tune the hyperparameters. The model was externally validated and compared with solitary pulmonary nodule models in an independent transnational cohort which comprised 220 patients treated in 6 Chinese and Korean hospitals from 2016 to 2018. Besides, a prospective comparison between the PKU-M model, clinicians, and a well-trained computer-aided diagnosis (CADx) system was conducted by using another registered multicentric cohort which comprised 78 patients treated in 4 Chinese hospitals from January 2019 to March 2019 (ClinicalTrials: NCT03795181).
The PKU-M model showed excellent discrimination [area under curve (AUC): 0.909 (0.854-0.946)] and calibration (brier score: 0.122). The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were 0.807, 0.849, 0.845, 0.811, and 0.828. External validation (583 nodules) revealed that the AUC of PKU-M model was [0.890 (0.859-0.916)], higher than that of the Brock model [0.806 (0.771-0.838)], PKU model [0.780 (0.743-0.817)], Mayo model [0.739 (0.697-0.776)], and VA model [0.682 (0.640-0.722)]. Prospective comparison (200 nodules) showed that the AUC of PKU-M model [0.871 (0.815-0.915)] was higher than the surgeons [0.790 (0.711-0.852), 0.741 (0.662-0.804), and 0.727 (0.650-0.788)], radiologist [0.748 (0.671-0.814)] and CADx system [0.757 (0.682-0.818)]. Furthermore, the model outperformed the clinicians with increase of 14.3% in sensitivity, and 7.8% in specificity.

After developed by machine learning algorithms, validated with transnational multicentric cohorts and prospectively compared to clinicians and CADx system, this first machine learning-based model for MPNs presented solid performance as a convenient reference to help decision-making.

**Keywords:** Lung cancer, Multiple pulmonary nodules, Prediction model, Machine learning
CORRELATION OF EGFR STATUS WITH CHEST CT SCAN FINDINGS AMONG PATIENTS WITH NON-SMALL CELL LUNG ADENOCARCINOMA: A SINGLE-CENTER RETROSPECTIVE COHORT STUDY

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An emerging avenue in oncologic imaging is radiogenomics, that is correlating imaging characteristics or “imaging phenotypes” with molecular phenotypes. Preliminary studies have shown an association of air bronchogram, pleural retraction, small lesion size and absence of fibrosis with EGFR mutation status and to the best of our knowledge, this is the first study in Filipino patients correlating EGFR status with CT scan findings.

A list of histologically diagnosed non-small cell lung adenocarcinoma (NSCLC) were reviewed and their non-contrast and contrast enhanced chest CT scan in axial and reconstructed sagittal and coronal images were obtained. A radiologist with a 10-year experience in reading chest CT scans was blinded to the EGFR results of the subjects. The dominant lung lesion was evaluated with fourteen parameters including site of the lesion, maximum diameter, shape, margin, density, presence or absence of air bronchograms, pleural retractions, intramucosal necrosis, satellite nodules, emphysema, pleural effusion, locoregional infiltration, lymphangitic carcinomatosis and lymphadenopathy. Results were tabulated and analyzed for presence of correlation.

A total of 47 patients (22 EGFR negative and 25 EGFR positive) with lung adenocarcinoma were included in the study. Most are females (55%) with an average age of 63 years old. Baseline chest CT scan of patients with biopsy proven NSCLC were reviewed for fourteen key findings. Among the clinical parameters and CT scan features, female gender (P value = 0.020), presence of air bronchograms (P value = 0.089 at 10% level of significance), lesions with extensions to more than 1 lobe (P value 0.019 at 5% level of significance) showed significant correlation with positive mutation status.

This study supported previous studies that EGFR positive tumors show significant correlation with the female gender and that these tumors are more likely to present as parenchymal lesions with air bronchograms. Further studies may be done to study to know the specific exon abnormalities in a Filipino population and correlate these with CT scan findings. Computer-assisted characterization of these tumors with their corresponding mutation status is also another promising study.

Keywords: EGFR, Radiogenomics, Non-small cell lung cancer
LUNG CANCER PROBABILITY AND CLINICAL OUTCOMES OF BASELINE AND NEW SUBSOLID NODULES DETECTED ON LOW-DOSE COMPUTED TOMOGRAPHY SCREENING

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Limited data are available on subsolid nodules detected on lung cancer screening with low-dose computed tomography (LDCT). We aimed to determine the characteristics of screen-detected subsolid nodules, and evaluate the probability of lung cancer and the clinical course of subsolid nodules detected at baseline and during follow-up screening.

We evaluated 50,132 (22,631 never-smokers and 27,501 ever-smokers) asymptomatic adults who underwent LDCT screening for lung cancer between May 2003 and June 2019 at a tertiary center in South Korea. The incidence, characteristics, and clinical outcomes of the baseline and new screen-detected subsolid nodules were determined.

A total of 6,725 subsolid nodules (5,116 pure ground glass opacity nodules and 1,609 part-solid nodules) were detected in 4,545 participants (1,484 new subsolid nodules detected in 937 [1.9%] participants; overall incidence of subsolid nodules: 10.7% in never-smokers and 7.7% in ever-smokers, p<0.001). Among 4,918 subsolid nodules that received follow-up with CT scans (mean number of CT scans including baseline LDCT: 4.6), 2,116 (43.0%, 30.0% of baseline subsolid nodules and 78.0% of new subsolid nodules) resolved spontaneously. Among 293 biopsied GGNs, 227 (77.5%) were diagnosed as lung cancer, of which 226 (99.6%) were adenocarcinomas. No significant difference was observed in pathological invasiveness or initial stage between the baseline and new cancerous subsolid nodules. Multivariate regression analyses revealed that detection at baseline screening was significantly associated with a higher probability of lung cancer (OR=3.95, 95% CI=2.32–6.74) and overall growth (OR=2.66, 95% CI=1.82–3.87), but a lower probability of resolution (OR=0.12, 95% CI=0.10–0.14).

LDCT screening led to a considerably high rate of subsolid nodule detection, particularly in never-smokers. Compared to the baseline subsolid nodules, the new subsolid nodules were associated with a lower probability of lung cancer and higher probability of spontaneous resolution, indicating their more inflammatory nature. Less aggres-
sive follow-up may be allowed for new subsolid nodules in future guidelines.

**Keywords:** Subsolid nodule, Ground-glass opacity nodule, Part-solid nodule, Lung cancer screening, Low dose computed tomography, Adenocarcinoma
RADIOLOGIC AND CLINICAL FEATURES OF SCREENING-DETECTED PULMONARY INVASIVE MUCINOUS ADENOCARCINOMA

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Invasive mucinous adenocarcinoma (IMA) is distinguished from non-mucinous adenocarcinoma with higher recurrence rate and poorer prognosis. The distinctive features of IMA had been suggested largely based on studies with advanced stage IMA and the data about whole spectrum of IMA are sparse, especially about early stage IMA. In this study, we evaluated the radiologic and clinical characteristics and the prognosis of screening-detected early stage IMA (SD-IMA).

Total of 93 patients who underwent curative surgery for screening-detected IMAs (≤3cm) from July 2013 to May 2019 were reviewed retrospectively. Data about radiologic characteristics, clinic-pathologic findings, and prognosis of all patients were obtained. The disease-free survival (DFS) was the primary endpoint for prognosis. The sensitivity of pretreatment histologic diagnosis and prognosis of SD-IMA were evaluated.

Majority of patients were female (62.4%, n=58) and non-smoker (74.2%, n=69). The mean age of patients was 64 ± 10.1 years. The dominant locations of screening-detected IMAs were both lower lobes (73.2%, n = 68) and one-quarter of tumors were located in other than lower lobes (right upper or middle lobe – 12 (12.9%), left upper lobe – 13 (14%)). Eighty-seven (93.5%) nodules were located in the periphery one-third of the lung and very close from visceral pleura (mean distance from visceral pleura was 2.4±5.0mm). The SD-IMAs are dominantly solid and high consolidation pattern nodule in CT findings. Radiologic features were part-solid nodule in 37 (39.8%) and solid nodule in 50 (55.7%). The sensitivity of preoperative tissue diagnosis was 61.1%. Extent of pulmonary resection were lobectomy in 70 (75.2%) patients. Pathologic stages of screening-detected IMAs were pIA in 72 (77.4%), pIB in 15 (16.1%). The median follow-up duration was 31 months (range: 1 - 73). Recurrences occurred in 6 patients (pleural seeding - 2, contralateral pulmonary metastasis - 3 and combined nodal recurrence and contralateral pulmonary and brain metastasis - 1). The patients who developed pleural seeding had been performed percutaneous needle biopsy before surgery. No death occurred during follow-up period. The 3 and 5-year DFS rates were 93.1 % and 88.2%.

SD-IMA was mostly presented as part-solid or solid nodule at peripheral portion of lung. The accuracy of histologic diagnosis of SD-IMA with small tissue samples or frozen examination was not high. The surgeons have to plan the surgical procedures with preoperative radiologic findings. SD-IMA showed favorable prognosis after surgical treatment including sublobar resection based on radiologic results.

Keywords: Invasive mucinous adenocarcinoma, Screening detection, Radiology
CHARACTERISTICS AND CLINICAL OUTCOMES OF PATIENTS WITH NON-SMOKING SMALL CELL LUNG CANCER IN KOREA

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Background/Aim: The aim of this study was to investigate the characteristics and clinical outcomes of patients with non-smoking small cell lung cancer (SCLC) using nationwide registry in Korea.

Methods: The Korean Association for Lung Cancer developed a registry in cooperation with the Korean Central Cancer registry (KCCR), and surveyed about 10% of lung cancer cases.

Results: From 2014 to 2016, the KCCR registered 1,043 patients newly diagnosed with SCLC. The median age was 71 years. The proportion of never-smokers was 14.8%, and never-smoking was more prevalent in women than in men (50.6% vs. 7.0%, P<0.001). The proportion of staging, performance status was not different between two groups, but the proportion of receiving palliative care was higher and that of receiving chemotherapy treatment was lower in non-smoking group. Overall survival (OS) was significantly shorter in non-smoking SCLC group (11.03 vs. 15.15 vs. 14.30 months, P = 0.001) than current and ex-smoker groups. OS was shorter in non-smoking group than ever-smoking group in SCLC(extensive-stage) patients (6.99 vs. 9.68 months, P = 0.004), but OS was not different between non-smoking and ever-smoking groups in SCLC(limited-stage) patients (19.4 vs. 23.5 months, P = 0.179). In a multivariate analysis using a Cox regression model, never smoking was not associated with OS, but older age, extensive stage, poor PS (ECOG ≥2), male, no prophylactic cranial irradiation (PCI) and no active treatment(chemotherapy and/or radiotherapy) were associated with poor prognosis. In subgroup analysis, never smoking was significantly associated with OS in limited-stage but not in extensive-stage patients.

Conclusion: Our study indicated that never-smokers are prevalent in SCLC in Korea. Never-smoking SCLC patients were older and tend to receive palliative care. Never-smoking SCLC patients had significantly shorter OS compared with smokers, and never smoking was significantly associated with poor OS in limited-stage SCLC patients.
### Keywords: Small cell lung carcinoma, Smoking

#### Subgroup analysis

<table>
<thead>
<tr>
<th>Factor</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P value</td>
<td>HR (95% CI)</td>
<td>P value</td>
</tr>
<tr>
<td>Age</td>
<td>1.049 (0.133-0.064)</td>
<td>&lt;0.001</td>
<td>1.007 (0.983-1.031)</td>
<td>0.595</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>1.215 (0.873-1.691)</td>
<td>0.249</td>
<td>1.863 (0.844-4.111)</td>
<td>0.124</td>
</tr>
<tr>
<td>Never smoking</td>
<td>1.260 (0.899-1.766)</td>
<td>0.180</td>
<td>2.410 (1.012-5.697)</td>
<td>0.047</td>
</tr>
<tr>
<td>NOD (≥2)</td>
<td>2.306 (1.612-3.300)</td>
<td>&lt;0.001</td>
<td>2.408 (0.984-5.894)</td>
<td>0.054</td>
</tr>
<tr>
<td>Symptom at diagnosis</td>
<td>1.914 (1.302-2.812)</td>
<td>0.001</td>
<td>2.082 (1.023-4.237)</td>
<td>0.043</td>
</tr>
<tr>
<td>POI</td>
<td>0.463 (0.296-0.726)</td>
<td>0.001</td>
<td>0.527 (0.320-0.868)</td>
<td>0.012</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>0.467 (0.359-0.608)</td>
<td>&lt;0.001</td>
<td>0.472 (0.295-0.755)</td>
<td>0.002</td>
</tr>
<tr>
<td>Chemo only</td>
<td>0.462 (0.389-0.548)</td>
<td>&lt;0.001</td>
<td>0.069 (0.018-0.273)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>2.062 (1.356-3.136)</td>
<td>&lt;0.001</td>
<td>1.831 (1.005-3.336)</td>
<td>0.048</td>
</tr>
<tr>
<td>Pleural nodules</td>
<td>1.334 (1.029-1.731)</td>
<td>0.030</td>
<td>1.167 (0.460-2.959)</td>
<td>0.745</td>
</tr>
<tr>
<td>Bone metastasis</td>
<td>1.373 (1.166-1.616)</td>
<td>&lt;0.001</td>
<td>1.544 (0.993-2.402)</td>
<td>0.054</td>
</tr>
<tr>
<td>Brain metastasis</td>
<td>0.897 (0.753-1.069)</td>
<td>0.223</td>
<td>1.675 (1.067-2.630)</td>
<td>0.025</td>
</tr>
<tr>
<td>Liver metastasis</td>
<td>1.728 (1.457-2.049)</td>
<td>&lt;0.001</td>
<td>2.251 (1.368-3.705)</td>
<td>0.001</td>
</tr>
<tr>
<td>Adrenal metastasis</td>
<td>1.128 (0.908-1.401)</td>
<td>0.276</td>
<td>1.648 (0.858-3.168)</td>
<td>0.134</td>
</tr>
</tbody>
</table>

![Log rank = 0.0072](image)
Pulmonary epithelioid hemangioendothelioma (PEH) is a rare vascular neoplasm with a varied presentation that can include multiple and bilateral lung nodules, for which the current literature is generally limited to case studies. This tumor is considered to be a borderline or low-grade malignancy with an unpredictable prognosis. Because a general consensus for the treatment of this rare tumor does not exist, we sought to utilize a large, national database to characterize the treatment patterns and outcomes.

Patients with malignant, non-metastatic PEH in the National Cancer Database between 2006-2017 were identified and stratified into groups based on treatment: observation, chemotherapy, and surgery. Univariate analyses were used to compare the groups, and survival was assessed using Kaplan-Meier curves and Cox-proportional hazards modelling.

A total of 92 patients with PEH were identified with an overall 5-year survival of 34.0%. Management included observation (n=28, 30.4%), chemotherapy (n=23, 25.0%) and surgical resection (n=41, 44.6%). Among the patients undergoing surgical resection for PEH, 26 (63.4%) underwent a wedge resection, 2 (4.8%) underwent a segmentectomy, 10 (24.3%) underwent a lobectomy, and 3 (7.3%) underwent a pneumonectomy. There were no differences in age, gender, Charlson comorbidity score, facility type, or tumor grade amongst the treatment groups. Median tumor size was larger for patients undergoing chemotherapy (3.85 cm [IQR: 3.45 - 4.40]) compared to those observed (2.30 cm [IQR: 1.53 - 4.23]) and those undergoing surgery (1.50 [IQR: 1.28 – 2.48]). Overall 5-year survival was 34.1%, 0%, 51.8% for the observation, chemotherapy, and surgery treatment groups, respectively (p < 0.001) (figure). Compared to those observed, patients undergoing chemotherapy had worse survival (HR 2.68, 95% CI: 1.38 - 5.23), however, there was no difference in survival with the surgery group (HR= 0.71 [95% CI: 0.33 -1.49]).

A diagnosis of PEH is associated with a generally poor prognosis in this national analysis. The finding that treat-
treatment with either systemic therapy or surgical resection did not improve survival beyond observation alone suggests that treatment with either modality should be reserved for patients having symptoms related to tumor mass or location.

**Keywords:** Pulmonary epithelioid hemangioendothelioma, Surgery, Chemotherapy, Observation, Outcomes, Survival

**Figure:** Overall survival of patients with pulmonary epithelioid hemangioendothelioma undergoing observation, chemotherapy, and surgery (log-rank p < 0.001).
USEFULNESS OF PULMONARY REHABILITATION IN NON-SMALL CELL LUNG CANCER BY ANALYZING PULMONARY FUNCTION TEST AND CHEST COMPUTED TOMOGRAPHY

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Pulmonary rehabilitation is useful in a variety of respiratory diseases and situations. We evaluate the usefulness of pulmonary rehabilitation in non-small cell lung cancer (NSCLC) patients undergoing surgery.

We retrospectively analyzed the medical records of 230 NSCLC patients undergoing surgery admitted to Korea University Guro Hospital between January 2018 and December 2019. Patients were divided into two groups according to pulmonary rehabilitation, and we analyzed pulmonary function test and chest computed tomography. Because the baseline characteristics were different between the two groups, we performed propensity score matching, additionally.

Of the 230 cases, 53 (23.0%) were in rehabilitation group and 177 (77.0%) were in control group. Before propensity score matching, lung function decreased lesser in the rehabilitation group than control. Forced expiratory volume in one second (FEV1) decreased to 9.3 ± 9.4% in the rehabilitation group, and to 19.5 ± 10.5% in the control group (P < 0.001). After propensity score matching, lung function also decreased lesser in the rehabilitation group. FEV1 decreased to 9.4 ± 8.4% in the rehabilitation group, and to 20.4 ± 9.0% in the control group (P < 0.001).

Pulmonary rehabilitation is useful in NSCLC patients undergoing surgery

Keywords: Rehabilitation, Surgery, NSCLC
Lung cancer surgery can lead to severe postoperative symptom burden for patients. We aimed to evaluate the efficacy of a patient-reported outcome (PRO)-based symptom management model to improve postoperative recovery of lung cancer patients.

We randomly assigned patients receiving the routine symptom management (routine group) or the PRO-based symptom management (intervention group) after lung cancer surgery at 3 Chinese hospitals between November 2019 and August 2020. Patients in the intervention group received interventions from the specialists when their reported target symptom (pain, fatigue, coughing, shortness of breath and disturbed sleep) scores reach the preset threshold (score ≥4) on the MD Anderson Symptom Inventory-Lung Cancer Module during the perioperative period. The primary outcome was mean symptom threshold events. The trial registration number was ChiCTR1900020846.

Among 166 patients allocated, 32 meeting the withdrawal criteria were excluded, resulting in 65 in the intervention group and 69 in the routine group. The intervention group reported less symptom threshold events than did the routine group (estimate, -0.36; 95% CI, -0.57 to -0.15; P<0.01). Symptom severity of pain (estimate, -0.48; 95% CI, -0.75 to -0.21; P<0.01), fatigue (estimate, -0.44; 95% CI, -0.70 to -0.18; P<0.01), and disturbed sleep (estimate, -0.35; 95% CI, -0.63 to -0.07; P=0.02) in the intervention group were significantly lower than in the routine group. Daily functioning of general activity (estimate, -0.67; 95% CI, -0.99 to -0.35; P<0.01), work (estimate, -0.65; 95% CI, -1.05 to -0.25; P<0.01), walking (estimate, -0.81; 95% CI, -1.14 to -0.48; P<0.01), mood (estimate, -0.62; 95% CI, -0.91 to -0.34; P<0.01), enjoyment of life (estimate, -0.38; 95% CI, -0.72 to -0.04; P=0.03), and relations with others (estimate, -0.40; 95% CI, -0.70 to -0.11; P=0.01) were significantly better in the intervention group than in the routine group.
Patients receiving PRO-based symptom management after lung cancer surgery have a better recovery.

Keywords: Patient-reported outcomes, Postoperative symptom, Lung cancer, Randomised controlled trial, Symptom recovery
Education Session IV.
Expanding the Surgical Indication in Lung Cancer

Chair: In Kyu Park (Korea)
Salvage Operation after Definitive CCRTx

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Department of Surgery, University of Chicago Hospital, Chicago, IL USA

Stage III non–small cell lung cancer (NSCLC) is a treatment challenge. Patients are treated for cure, but cure is elusive, and acceptable treatment plans vary dramatically. Chemotherapy-based multimodality is the standard of care, but ideal local therapy is debated. Diversity in treatment approaches results in salvage resections. These are resections performed after curative intent concurrent chemoradiotherapy in patients initially excluded from surgery and occur > 12 weeks form completion of therapy. The reasons that patients are not offered surgery are often based on institutional bias rather than extent of disease. Salvage resection patients fall into 3 broad categories: (1) those who have relapsed, with clear evidence for primary tumor regrowth after an initial treatment response, (2) those with persistent disease, who transition from bimodality to trimodality therapy when review of the staging (usually by a different treatment team) determines resectability, even though surgery was excluded from primary treatment approach, and (3) those who present for treatment related complications such as abscess or bronchopleural fistula. The distinction between these presentations impacts both short- and long-term outcomes, those with persistent disease have improved survival (median: 36-43 months) compared with those with relapse or complication (median: 9-12 months). A common characteristic of salvage resections is they frequently occur in patients are diagnosed and initially treated at a separate institution from the eventual surgical team, and the surgical team was not involved in the original treatment decision. This increases the uncertainty of initial staging procedures and introduces an undesirable delay between induction therapy and resection. Salvage resections are associate with increased morbidity and mortality, and decreased overall survival compared to planned resections after induction therapy for the same stage disease, therefor careful patient selection is imperative. Immunotherapy in the form of checkpoint inhibitors have dramatically altered the treatment of stage IV disease and are now being used in stage III. They may significantly impact the treatment landscape before, after, or in lieu of surgery.
Salvage Surgery for Advanced Non-small Cell Lung Cancer after Targeted Therapy

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Molecular targeted therapy has been widely adopted as a key treatment for stage IV and stage non-small cell lung cancer (NSCLC) harboring druggable driver oncogene abnormalities, including epidermal growth factor receptor (EGFR) mutations and anaplastic lymphoma kinase (ALK) rearrangement. Targeted therapy provides a highly effective clinical response for NSCLC with driver oncogene abnormalities, and some patients who receive TKI for unresectable stage IIIB-IV NSCLC experience dramatic down-staging to resectable N0M0 disease or isolated progression localized in the primary lesion under the control of other lesions. Targeted therapy is basically cytostatic and cannot to cure the disease despite the initial dramatic clinical response. Residual primary lesion usually contains cancer cells resistant to currently administered TKI. Progression indicates apparent resistance to TKI treatment even if the progression site is limited to the primary lesion. Thus, surgical removal of residual or regrown primary lesion, “salvage surgery”, after TKI may be a treatment of choice for eradicating persistent or multiplying cancer cells that are resistant to TKI and improving survival. Recent reports and our experience have indicated that salvage surgery after TKI is feasible, but surgery is technically demanding, especially if the initial metastatic lymph nodes are close to critical anatomical structures including pulmonary artery, due to the scar-like formation caused by targeted therapy. Optimal indications and timing of “salvage surgery” after TKI should be evaluated in future studies.
The immunotherapy has changed the treatment modes for advanced non-small cell lung cancer (NSCLC), moving from second-line to first-line treatment and significantly increasing patients’ survival. Surgery and chemo-radiotherapy remain the mainstay of the treatment for patients with locally advanced lung cancer, but recurrence and metastasis still occur in some patients. The survival rates of conventional perioperative chemotherapy among NSCLC patients have increased by only 5%. Therefore, recent clinical trials have begun to explore targeted and immune neoadjuvant therapies in early-stage and locally advanced NSCLC, and the relevant clinical research studies have shown good efficacy, safety profiles and surgical outcomes. In this presentation, the recent clinical trials on neoadjuvant immunotherapy followed by surgery will be summarized and the potential biomarkers for the response to the immunotherapy will be discussed.
Pulmonary Resection after Neoadjuvant Therapy

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Department of Thoracic and Cardiovascular Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

The optimal treatment for stage IIIA-N2 non-small cell lung cancer (NSCLC) is controversial. The prognosis after only local therapies, such as surgery or radiotherapy, is unacceptable despite the locally advanced stage of this disease subset. The reason for this poor prognosis may be related to the presence of occult microscopic systemic metastases in some patients with N2 disease at initial presentation. Thus, clinicians and researchers have been focusing on multimodal therapies, which include systemic therapies, such as chemotherapy. Despite many clinical trials, the optimal multimodal therapeutic approach, such as neoadjuvant chemotherapy or neoadjuvant chemoradiotherapy followed by surgery and definitive concurrent chemoradiotherapy, is still unclear. Indeed, the role of surgery in local control has not yet been established; pivotal randomized controlled trials failed to show a survival benefit from surgery over radiotherapy. Therefore, when considering surgery as a component of multimodal treatment for stage IIIA-N2 NSCLC, we should keep in mind the following factors that affect outcomes: (1) optimal candidate, (2) optimal regimen, and (3) optimal surgical technique.

Theoretically, patients with good prognostic factors are optimal candidates for surgery after neoadjuvant therapy. Most studies indicate that mediastinal downstaging and complete surgical resection are the most important surrogate markers of survival. Compared with bulky, multiple station N2 disease, patients with non-bulky, single station N2 metastases are more likely to undergo mediastinal downstaging and complete surgical resection. The best methods to evaluate mediastinal downstaging prior to surgery are mediastinal restaging, such as imaging studies, minimally invasive needle biopsy or surgical restaging techniques. However, these methods are often inaccurate and not feasible. The likelihood of developing postoperative morbidities and mortalities should also be considered when identifying optimal candidates. Patients with good performance status and less underlying comorbidities are more likely to tolerate the surgical insult following neoadjuvant therapy.

Regarding optimal regimens, many factors should be considered, including radiotherapy as a preoperative treatment modality, the radiotherapy regimen (radiation dosage, schedule, sequential vs. concurrent, IMRT vs. 3DCRT,
etc.), the chemotherapy regimen, and the timing of surgery. Neoadjuvant concurrent chemoradiotherapy plus surgery may provide the best chance for mediastinal downstaging. However, the therapeutic effect of this approach is offset by the serious treatment-related toxicities and early postoperative mortalities, especially after pneumonectomy. Of note, most studies comparing neoadjuvant chemotherapy to neoadjuvant chemoradiotherapy observed no significant differences in survival despite the higher rate of mediastinal downstaging in neoadjuvant concurrent chemoradiotherapy.

Pneumonectomy after neoadjuvant therapy, especially concurrent chemoradiotherapy results in higher postoperative mortality according to the results of previous clinical trials. Thus, the selection of patients who only need lobectomy is critical. Sleeve lobectomy is a good alternative to avoid pneumonectomy. However, morbidities related to anastomosis failure after sleeve resection, are significant, especially after chemoradiotherapy. Of note, adequate lymph node assessment can be challenging after neoadjuvant therapy. Suboptimal mediastinal lymph node dissection should be regarded as uncertain in terms of the newly proposed R categories.

Neoadjuvant treatment has many advantages: (1) pathological downstaging and evaluation of tumor sensitivity in vivo are possible, (2) better local control facilitates radical surgery by decreasing the tumor volume, (3) clinically undetected micrometastatic disease may be eradicated, and (4) tolerance is better compared to adjuvant chemotherapy with the administration of higher full doses and more cycles. Nonetheless, these advantages will be offset if the surgical resection leads to incomplete resection or higher postoperative mortalities. To enhance the treatment outcomes of surgery after neoadjuvant therapy, the best candidates should be identified, regimens should be refined, and the best surgical techniques should be pursued.
Education Session V.
Advances in Radiation Oncology

Chair: Hong-Gyun Wu (Korea)
Circulating Tumor DNA as a Therapeutic Marker after Radiotherapy

Scott Bratman
University of Toronto, USA
Combining of Radiotherapy with Immunotherapy in NSCLC

Joo Ho Lee
Department of Radiation Oncology, Seoul National University Hospital, Seoul, Korea

Radiotherapy plays a pivotal role in the treatment of non-small cell lung cancer (NSCLC). The success of immune checkpoint inhibitors (ICIs) in metastatic NSCLC has led to an interest in moving ICIs into the curative setting in locally advanced NSCLC. The PACIFIC data encourages the usage of consolidative durvalumab after completion of concurrent chemoradiotherapy in patients with locally advanced NSCLC. This data raised the following studies testing other ICIs for concurrent chemoradiotherapy, and the optimal role of radiotherapy for combination with ICIs. Also, for early-stage NSCLC or oligo-metastasis of NSCLC, with the advances in radiotherapy, stereotactic radiotherapy can intensify the radiation to the focal area with preserving the immune system. In addition to the well-established tumoricidal effect of radiation, radiotherapy is emerging as immune-modulating options in the era of ICIs. This presentation will explore the preclinical and clinical evidence supporting the immune-modulating role of radiotherapy. Then, the current status of the combination of radiotherapy with immunotherapy will be reviewed, including the debates and future direction in the view of radiation oncology.
Proton beam therapy (PBT) has unique physical property which stops at a certain depth with a very sharp dose gradient. Therefore, PBT can decrease dose to organs at risk, and then reduce radiation-related toxicity.\(^1\) \(^3\) But PBT is sensitive to respiratory motion and this technical challenge limits wide application of PBT in lung cancer. The Particle Therapy Co-operative Group (PTCOG) Thoracic Subcommittee task group reviewed the potentials and limitations of PBT in lung cancer, and suggested clinical scenarios beneficial to PBT.\(^1\) In this review, larger tumors, central tumors, tumors near the brachial plexus, and multiple tumors are suggested potential indications for PBT.

In early-stage non-small cell lung cancer (NSCLC), a systematic-review and meta-analysis demonstrated survival improvement after PBT compared with stereotactic body radiotherapy (SBRT), while patterns of failures were comparable.\(^4\) But, the survival difference was not significant after adjusting for operability. As we expected, PBT reduced grade ≥3 radiation pneumonitis. In contrast, grade ≥3 chest wall toxicity and rib fractures were increased after PBT. Because patients with underlying lung disease, especially idiopathic pulmonary fibrosis (IPF), experienced severe pulmonary toxicity after radiotherapy frequently, they might be potential candidates for PBT.\(^5\) Our retrospective comparison of PBT and X-ray showed that PBT reduced acute and fatal complication in patients with NSCLC who had IPF.\(^6\) Then, prospective of PBT for lung cancer with underlying lung disease has been conducted.

In locally-advanced NSCLC, one prospective randomized trial compared intensity modulated radiation therapy (IMRT) vs. passively scattering proton therapy (PSPT).\(^7\) PBT did not reduce grade ≥3 radiation pneumonitis, while local failure was same. Intensity modulated proton therapy (IMPT), which uses active scanning beams, might be a future alternative.\(^8\) \(^10\) Compared with IMRT, IMPT resulted in similar outcomes in a frailer population, and a trend toward lower rates of pneumonitis after IMPT was also observed.\(^8\) \(^9\) Similarly, our retrospective comparison also showed that IMPT reduced grade ≥2 radiation pneumonitis, although patients treated with IMPT had worse pulmonary function. But grade ≥3 radiation esophagitis was increased after IMPT.
Another potential candidate for PBT is reirradiation for recurrent lung cancer. As higher composite dose is associated with greater toxicity, PBT could be feasible in terms of reducing dose to organs at risk.\textsuperscript{11} While one multi-institutional prospective study showed significant toxicity,\textsuperscript{12} recent prospective registry study showed that acute and late toxicities occurred in 6% and 1%, respectively.\textsuperscript{11} Another retrospective study using IMPT for reirradiation showed that late grade 3 pulmonary toxicity was developed in 7% of patients.

In summary, PBT may be able to give better outcome in lung cancer patients, especially in patients with underlying lung disease such as IPF. IMPT may be beneficial for lung cancer with complex shape, and recurrent disease within previous radiation field.

References

Molecular targeted therapy (MTT) is effectively applied to patients stratified by checking gene mutations such as epidermal growth factor receptor (EGFR) mutations based on invasive biopsy. However, standard treatment approaches except the MTT have not always been effective for all patients. For instance, the patients with stage I or II non-small cell lung cancer (NSCLC) may have two options, i.e., surgery or stereotactic body radiation therapy (SBRT), because expected outcomes of those two treatment options are almost the same (around a 5-year survival rate of 70%). As long as lung cancer patients do not refuse the surgery or they are operable, physicians should weight up the two options in a same stage, and more appropriate treatment approach should be selected from the two options.

The radiomics with artificial intelligence (radiomics-AI) could attempt to solve the issue by providing us the chances to choose more appropriate treatment approaches prior to patients’ treatments based on non-invasive pre-treatment images. The purpose of the radiomics-AI is to stratify cancer patients into cancer subtypes according to the AI (machine learning) output. The key point in the radiomics-AI is to find a signature (a set of significant image features related to what you want to predict) for each branch of a cancer treatment flowchart. We assume that image features could mathematically characterize the heterogeneity of tumors in medical images, which could be associated with the patients’ prognoses.

This lecture will introduce the background, basic idea, overall framework, frontlines, and future of radiomics based on many references.
Satellite Symposium II.
Pfizer Ltd.

Chair: Jin Seok Ahn (Korea)
Activating mutation of EGFR is one of the most common targetable driver gene alterations in NSCLC. Over the last decade, many tyrosine kinase inhibitors have been approved for the front line treatment of EGFRm NSCL that are grouped by 1st, 2nd, and third generation according to the mechanism of action and ability for overcoming some of the resistant mutations.

Dacomitinib is one of the second generation EGFR-TKIs that irreversibly bind to EGFR and recently approved from many countries for the treatment of NSCLC with activating EGFR mutations. In phase III, ARCHER-1050 trial, dacomitinib showed an improved overall survival [34.1 vs 27.0 months, HR 0.748 (95% CI 0.591-0.947), p = 0.0155] as well as a superior PFS [14.7 vs 9.2 months, HR 0.59 (95% CI 0.47-0.74), p<0.0001], when compared to the 1st generation gefitinib. Subgroup analyses revealed that this superior tendency was observed across most of the subgroups including race of participants and mutation type of EGFR. Osimertinib, a third generation EGFR-TKI, was developed targeting EGFR T790M resistant mutation. In phase III, FLAURA trial, osimertinib also has shown a survival [38.6 vs 31.8 months, HR 0.80 (95.05% CI 0.64-1.00, p=0.046)]/PFS [18.9 vs 10.2 months, HR 0.46 (95% CI 0.37-0.57)] benefit compared with the first generation TKIs (gefitinib/erlotinib) as the front line treatment.

Increasing number of available drugs for the treatment of EGFRm NSCLC inevitably evoked an issue about the choice of the front line drug or the optimal sequence of treatment for these patients. In daily clinical practice, multiple factors including clinical characteristics of the patients, availability of various treatment options after progression as well as the local reimbursement system could be taken into consideration for the right selection of the first line treatment.
Satellite Symposium III.
Ono Pharma Korea / BMS Korea

Chair: Ji Youn Han (Korea)
Nivolumab (NIVO) + ipilimumab (IPI) have distinct but complementary mechanisms of action, and have shown improved long-term survival in melanoma, RCC, and NSCLC. IPI induces de novo anti-tumor T-cell responses, including an increase in memory T cells, while NIVO restores anti-tumor T-cell function. Here are the recent results of study of dual immunotherapy with NIVO+IPI.

CheckMate 227 showed durable response and OS benefit with NIVO + IPI versus chemotherapy in first-line (1L) advanced NSCLC, regardless of histology or PD-L1 expression. With 3-years minimum follow-up, 1L NIVO + IPI continued to provide durable and long-term efficacy benefits versus chemotherapy for patients with advanced NSCLC, regardless of PD-L1 expression (3-year OS rates: 33% vs 22% (PD-L1 ≥ 1%), 34% vs 15% (PD-L1 < 1%)).

Especially, over one-third of all responders remained in response after 3 years with NIVO + IPI vs < 5% with chemotherapy. Among patients with PD-L1 ≥ 1%, 70% of responders at 6 months in NIVO + IPI arm were alive 3 years later vs 39% in chemo arm; similar findings were observed in patients with PD-L1 < 1% (exploratory post-landmark OS analysis). No new safety signals were identified for NIVO + IPI with extended follow-up.

CheckMate 9LA (NCT03215706) is a phase 3 randomized open-label study evaluating NIVO + IPI + chemo (2 cycles) vs chemo (4 cycles) in 1L stage IV or recurrent NSCLC. Adding a limited course of platinum-doublet chemotherapy (chemo) to the first few weeks of NIVO + IPI was hypothesized to provide rapid disease control while building on the durable survival benefit provided by NIVO + IPI in 1L NSCLC as observed in CheckMate 227. CheckMate 9LA met its primary endpoint of OS at the pre-planned interim analysis (HR 0.69, P = 0.0006). Clinically meaningful improvement of all efficacy endpoints was observed and increased with longer follow-up. With a minimum follow-up of 12 months, OS benefit was further improved (HR 0.66). Magnitude of benefit with NIVO + IPI + 2 cycles of chemo vs chemo was consistent across histologies and all PD-L1 expression levels, including PD-L1 < 1% and 1-49% populations. There were no new safety signals were observed for NIVO + IPI + 2 cycles of chemotherapy. With early separation of OS curves and lower progressive disease rates as best of response, the hypothesis for CheckMate 9LA study design was validated. CheckMate 9LA demonstrated that NIVO + IPI with a limited course of chemo should be considered as a new first-line treatment option for advanced NSCLC.
Multidisciplinary Symposium.
SABR versus Surgery for Early Lung Cancer

Chair: Dong Kwan Kim (Korea)
Early-stage (T1-2 N0) non-small cell lung cancer (NSCLC) may steadily increase with implementation of low-dose computed tomography (LD-CT) screening programs. Radiotherapy (RT) was historically used for the patients who were not feasible to surgical resection. Over the past two decades, technological developments in RT have allowed development and implementation of SABR, which uses very high ablative radiation doses in 1 to 5 fractions with highly conformal techniques.

The first reports on lungs SABR appeared in the mid-1990s, primarily from Japan and Europe. With the accumulated evidence, SABR emerged as standard of care for medically inoperable, peripheral early-stage NSCLC. However, majority of original studies comparing surgery vs. SABR are largely retrospective cohort studies and single institutional reports. Moreover, recently published meta-analyses performed quantitative synthesis of pooled data mostly from retrospective studies. Therefore, were not free of a number of biases inherent to retrospective studies. Also, significant variation remains for other clinical scenarios. SABR for patients who are medically operable or lack tissue confirmation also remains controversial. Since the publication of a pooled analysis of two randomized trials in Lancet Oncology in 2015, there have been to date no supporting results from other prospective trials for 5 years.

Systematic review by Cao et al. included 32 studies with pooled analysis of STARS and ROSEL trials and 31 observational studies that included SEER (n=6) and NCDB (n=3) analyses. Primary endpoint was overall survival in matched and unmatched cohort, and secondary endpoints were CSS, DFS, FFRR, FDR, perioperative mortality and morbidity. The study primary endpoint of OS, along with secondary endpoints of CSS, DFS and FLRR, were all strongly in favor of surgical resection (OS: OR 1.71, 95% CI: 1.52–1.94, P<0.00001; CSS: OR 1.78, 95% CI: 1.28–2.48, <0.0006; DFS: OR 1.83, 95% CI: 1.06–3.16, P=0.03; FLRR: OR 2.91, 95% CI: 1.49–5.71, P=0.002). As expected, periprocedural mortality was less after SBRT than with surgery (0% SBRT versus 0–8% surgery). Several trials with SABR biologically equivalent dose were less than 100 Gy.
The current evidence suggests surgery is superior to SABR in terms of mid- and long-term clinical outcomes. SABR is associated with lower perioperative mortality. Improved outcomes after surgery may be due at least in part to an imbalance of baseline characteristics. Furthermore, the most studies comparing SABR vs. surgery are likely underpowered, even some studies included many patients treated before 2010, which was outdated. Meta-analysis use diverse cohorts with very different patient and tumor characteristics, limiting the reliability of their conclusions.

In conclusion, SABR has an important role to play in treating early-stage NSCLC, particularly for medically inoperable patients with limited other treatment options. The current evidence from meta-analysis and real world data suggests that surgery is associated with better survival than SABR, but SABR has a lower rate of higher toxicity and better quality of life, which may account for the preference of SABR among some patients. Shared decision-making with patients should be performed in all cases to ensure the patient understands the risks related to SABR, the side effects, and the alternative treatments available. Future studies should aim to provide histopathologic confirmation of malignancy and compare SABR with minimally invasive anatomical resections.
Surgery as a Primary Treatment for Early Lung

Masatsugu Hamaji
Department of Thoracic surgery, Kyoto University, Kyoto, Japan

For good-risk operable patients with early stage non-small cell lung cancer (NSCLC), lobectomy and mediastinal lymph node dissection is the standard treatment of choice. Stereotactic body radiotherapy (SBRT) may be a potential alternative to surgical resection in high-risk operable patients with early-stage NSCLC. Herein, comparisons between surgery and SBRT using propensity-score matching in patients of Kyoto University Hospital are discussed in detail. Relatively new surgical technologies, which have been applied to early-stage NSCLC are also introduced in detail.
SABR as a Primary Treatment for Early Lung Cancer

Jaeho Cho
Department of Radiation Oncology, Yonsei University College of Medicine, Seoul, South Korea

Stereotactic ablative radiotherapy (SABR) is a novel method that delivers an ablative dose of radiation to the treatment targets with high accuracy. In early stage non-small cell lung cancer (NSCLC), SABR has shown excellent local control with minimal toxicity. The impressive clinical efficacy of SABR is greater than that expected by the linear quadratic model and the conventional radiobiological principles, i.e. 4 R’s of radiobiology (re-oxygenation, repair, re-distribution, and repopulation), which is no longer suitable for the explanation of SABR’s ablation effects. Currently there are no data based on a randomized controlled trial for c-stage I NSCLC comparing surgery with SBRT using a large sample size and long observation period. So far multiple studies have suggested therapeutic equipoise exists between SABR and surgery in low-risk or high-risk operable patients with early stage NSCLC. Recent propensity score-matching analyses revealed that the overall survival and disease free survival for patients with c-stage I NSCLC in the surgery group were slightly superior to those for those in the SBRT group, but the survival were not significantly different between the two therapeutic approaches. These two very good treatment options for c-stage I NSCLC require a shared decision-making (SDM) process that provides enough information to patients about the pros and cons of each treatment. The information and factors that patients need to determine the right treatment for them include a variety of factors such as survival outcome, side effects, treatment cost, duration of treatment and recovery, convenience of treatment, their age, patient’s morbidity, patient’s performance status, confidence in the medical staff and so on. In addition to those mentioned above, this presentation will also cover the rescue treatment for post-SABR recurrence, patterns of failure after SABR, and which patients benefit most from SABR in medically operable NSCLC.
Combination of SABR and Immunotherapy for Lung Cancer

Joe Y. Chang
Radiation Oncology, MD Anderson Cancer Center, Houston, Texas, USA

Stereotactic Ablative Radiotherapy (SABR) provides >95% local control and has become the standard of care for medically inoperable stage I NSCLC and an option for operable stage I NSCLC. However, cumulatively about 30-40% of patients develop recurrence in the regional lymph nodes, distant organs, or secondary lung cancer. Combined immunotherapy and SABR (I-SABR) may reduce these recurrences by stimulating a stronger cancer specific immune response.¹

We are conducting a phase II randomized study (SABR vs. I-SABR using Nivolumab) to evaluate the efficacy and toxicity of I-SABR in medically inoperable, early stage or isolated recurrence NSCLC without lymph node or distant metastasis. We reported interim analysis of toxicity. 92 patients (median age: 72, range: 57 to 90) were enrolled and randomized. Combined immunotherapy and SABR (I-SABR) appear to be well-tolerated in this fragile patient population with no grade 4/5 toxicity.

For patients with metastatic NSCLC, local ablative therapy has been shown to improve PFS and OS in patients with oligo-metastasis (<3 sites) in phase II randomized studies. The role and optimal strategies of local therapy in patients with more than 3 sites of metastasis is being investigated.² Compared with immunotherapy alone, preliminary data indicated that I-SABR appears to improve PFS and OS in pooled phase II randomized studies. A phase III randomized study to compare Nivolumab/Ipilimumab with/without local ablative therapy (or surgery) is ongoing.

I-SABR approach opens a novel research field to improve local/systemic control and OS in early and metastatic NSCLC.

References

MSIO Joint Session.
Immunotherapy in Different Clinical Situations: What’s the Optimal Approach?

Chair: Sang-We Kim (Korea)
Case 1. Newly Diagnosed Advanced and Metastatic Adenocarcinoma of the Lung

Case 2. Newly Diagnosed Locally Advanced Non-Small Cell Lung Cancer but Multiple Nodal Stations

Case 3. Newly Diagnosed Early Lung Cancer but Comorbidities

Dae Ho Lee
Department of Oncology, University of Ulsan Asan Medical Center, Seoul, Korea

Immunotherapy becomes one of the standards for non-small cell lung cancer. The success of immune checkpoint inhibitors (ICIs) has started in previously treated patient with advanced or metastatic NSCLC as monotherapy. As more successes with different ICI treatment approaches followed in different clinical situations, the indications are rapidly expanding, for example, different combinations as first-line therapy, consolidation therapy after definitive chemoradiotherapy or adjuvant/neo-adjuvant therapy with surgery. However, still many patients do not benefit from ICIs or lose the benefits due to disease progression, unacceptable toxicities or even comorbidity. In addition, oncogene-driven personalized medicine might be a more appropriate option for some NSCLC patients rather than immunotherapy. Today, we will discuss the cases about the challenges faced during ICI treatment in different clinical situations and try to get ideas or insights about how to optimize the treatment and what to know for future NSCLC patients.
Plenary Session I.

Chair: Young Tae Kim (Korea)
Increasing evidence supports complex subclonal relationships in solid tumours, manifested as intratumour heterogeneity. Parallel evolution of subclones, with distinct somatic events occurring in the same gene, signal transduction pathway or protein complex, suggests constraints to tumour evolution that might be therapeutically exploitable. Data from TRACERx, a longitudinal lung cancer evolution study will be presented. Drivers of tumour heterogeneity change during the disease course and contribute to the temporally distinct origins of lung cancer driver events. APOBEC driven mutagenesis appears to be enriched in subclones in multiple tumour types. Oncogene, tumour suppressor gene and drug induced DNA replication stress are found to drive APOBEC mutagenesis. Phylogenetic tracking detects minimal residual disease and clonal evolution of disease from primary to metastatic sites, presenting opportunities for drug development.

On-going chromosomal instability, manifested as Mirrored Subclonal Allelic Imbalance (MSAI) is found to be a major driver of intratumour heterogeneity across cancer types, contributing to parallel evolution and selection. The finding of subclonal driver events, evidence of ongoing selection within subclones, combined with genome instability driving cell-to-cell variation is likely to limit the efficacy of targeted monotherapies, suggesting the need for new approaches to drug development and clinical trial design and integration of cancer immunotherapeutic approaches. Multiple adaptive mechanisms to neo-antigen evolution have been found in TRACERx that emphasise the role of cancer chromosomal instability driving immune evasion and HLA/MHC loss and loss of clonal neo-antigens as well as epigenetic repression of neo-antigens. The clonal neo-antigenic architecture may act as a tumour vulnerability, targeting multiple clonal neo-antigens present in each tumour to mitigate resistance and treatment failure.
Plenary Session II.

Chair: Jeong-Seon Ryu (Korea)
10-Year and Beyond Results in NELSON Lung Cancer Screening Study

Harry J. de Koning
Department of Public Health, Erasmus MC, Rotterdam The Netherlands

- The step-wise decision-making concerning potential new cancer screening programmes include the establishment of evidence of effectiveness, benefits that outweigh the harms, and cost-effectiveness.

In: European Guidelines on Quality Improvement in Comprehensive Cancer Control (2013) by T. Alberti, R. Rosavec & M. van der Bilt
Reduced Lung-Cancer Mortality with Volume CT Screening in a Randomized Trial


**NELSON trial**

- Randomized Controlled Trial
- Recruitment through population-based registries
- CT screening vs. no screening
- Different screening intervals
- Volume & Volume Doubling Time of nodules
- Central reading of CT images
- Expert causes of death committee
- Follow-up through national registries

Trial, initially powered (80%) for high risk males, to detect a lung cancer mortality reduction of 2.23% after 10 years after randomization (individual F1) in ages 55-74 and includes a small subgroup of women (19%)

**NELSON trial (males)**

3.3% were referred to a pathologist for work-up and diagnosis. Screening detected lung cancer in 0.3%.

**Screening Test Results in Male Participants**

<table>
<thead>
<tr>
<th>Screening Test Results in Male Participants</th>
<th>Male (n=1,800)</th>
<th>Female (n=1,800)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detection of Lung Cancer</td>
<td>113 (0.62%)</td>
<td>30 (0.17%)</td>
</tr>
<tr>
<td>Positive Predictive Value</td>
<td>45.1%</td>
<td>34.1%</td>
</tr>
<tr>
<td>Negative Predictive Value</td>
<td>82.5%</td>
<td>89.5%</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>98.1%</td>
<td>99.6%</td>
</tr>
<tr>
<td>Specificity</td>
<td>73.3%</td>
<td>75.7%</td>
</tr>
</tbody>
</table>

Table 1: Screening Test Results in Male Participants
Harry J. de Koning | 10-Year and Beyond Results in NELSON Lung Cancer Screening Study

Message indeterminate screening test result

“We have observed a very small abnormality in your lung (5-10 mm long).
Such a small abnormality is often detected in many persons and it usually
represents a small scar or a minor inflammation. Therefore, at this moment
there is no need for any further investigations. However, in order to see
whether there has been any change in this abnormality, a new CT scan of
the lungs will be made after 3 to 4 months.”

Lung-Cancer Incidence in Male Participants

Lung-Cancer Incidence at 10 years of follow-up
- 5.58 cases per 1000 person-years in the screening group
- 4.91 cases per 1000 person-years in the control group

Lung-Cancer Mortality in Male Participants

Lung-Cancer Mortality at 10 years of follow-up (from incidence data)
- 2.50 deaths per 1000 person-years in the screening group
- 3.30 deaths per 1000 person-years in the control group

Cumulative RR: 0.76 (95% CI: 0.61-0.94)

Stage Shift NELSON males

Out of 341 lung cancers found
- I (60%)
- II (13%)
- III (23%)
- IV (4%)
Subgroup analysis: per age group
in male NELSON participants

<table>
<thead>
<tr>
<th>Age group</th>
<th>Lung cancer deaths</th>
<th>NELSON rate (%)</th>
<th>Rescaled (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-39</td>
<td>15</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>40-49</td>
<td>31</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>50-59</td>
<td>40</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>60-69</td>
<td>40</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>70-79</td>
<td>40</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>80+</td>
<td>40</td>
<td>0.01</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Small subgroups with statistical differences

- Symptoms, signs, and abnormal clinical findings, otherwise not specified (n=57)
- Endocrine, nutritional and metabolic diseases (n=30)

ONLY one lung cancer confirmed: reviewed by expert committee (NOT LC)
ONLY 3 with a (false positive) CT scan result: death at least 16 months later

Lung cancer mortality rate ratio (95% CI)

<table>
<thead>
<tr>
<th></th>
<th>Year 7</th>
<th>Year 8</th>
<th>Year 9</th>
<th>Year 10</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MALES</strong></td>
<td>0.76</td>
<td>0.76</td>
<td>0.76</td>
<td>0.76</td>
</tr>
<tr>
<td></td>
<td>(0.65-0.87)</td>
<td>(0.61-0.90)</td>
<td>(0.61-0.94)</td>
<td></td>
</tr>
<tr>
<td><strong>FEMALES</strong></td>
<td>0.46</td>
<td>0.41</td>
<td>0.52</td>
<td>0.67</td>
</tr>
<tr>
<td></td>
<td>(0.27-0.62)</td>
<td>(0.19-0.84)</td>
<td>(0.28-1.04)</td>
<td></td>
</tr>
</tbody>
</table>

Cumulative Numbers of Lung Cancers and of Deaths from Lung Cancer NLSET

<table>
<thead>
<tr>
<th></th>
<th>Deaths from Lung Cancers</th>
</tr>
</thead>
<tbody>
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<td></td>
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</table>

Korean Association for Lung Cancer
**Lung cancer mortality rate ratio (95% CI)**

<table>
<thead>
<tr>
<th>Year</th>
<th>NELSON</th>
<th>NLST</th>
<th>NLST-eligible in NELSON</th>
</tr>
</thead>
<tbody>
<tr>
<td>MALES</td>
<td>0.76 (0.59-1.04)</td>
<td>0.92</td>
<td>0.78 (0.59-1.04)</td>
</tr>
<tr>
<td>FEMALES</td>
<td>0.41 (0.34-1.00)</td>
<td>0.73</td>
<td>0.37 (0.14-0.89)</td>
</tr>
</tbody>
</table>

**Power analysis**

**All-Cause Mortality NELSON males**

Figure 5b: The cumulative all-cause mortality rate (per 1,000) per year since randomization.

**WHAT NEXT**

- For lung cancer screening, the evidence on effectiveness, benefits that outweigh the harms, and cost-effectiveness is now firm.
- Once evidence exists to support these criteria, implementation research in each country is needed to assess the feasibility of fulfilling the national requirements in practice.
Harry J. de Koning | 10-Year and Beyond Results in NELSON Lung Cancer Screening Study

**Missing Pieces of Information**
- Lung cancer screening means personalised, risk-based approaches
- Health care systems’ implementation of personalised screening and prevention is still sparse, and likely to be of variable quality
  
  → Important issues have to be addressed to ensure effective and high-quality implementation, such as:

**Tailored Recruitment**
- Recruitment Challenge
  - Need for adequate (self) selection based on risk assessment
  - Low participation rates among individuals in the more deprived socioeconomic groups (SES), although lung cancer risk is elevated in these groups.
  - Factors relating to eligibility for lung cancer screening differ greatly from the factors associated with (intermediate) lung cancer screening uptake
  - No one-size-fits-all approach
  
  → Need more evidence about:
  1. The information needs per subgroup of the general (high-risk) population
  2. Potential reachable moments to contact/reach potential eligibles
  3. Preferences regarding the media of recruitment materials (e.g., letter, brochure, online information, interactive websites, call center, health care provider)

**Risk-Based Eligibility**
- Prevent screening of the low-risk (but anxiety?) population
  - Example: PLCO<sub>optimal</sub> 2.5% vs. 1.0%
  
  → Thresholds yield a smaller number of LYG as
  - USPSTF criteria, but requires 5% less CT screens

- Risk-based strategies more likely to recruit older individuals and groups with diminished life-expectancy
  - More research needed to identify the optimal thresholds for risk-based selection

- How do we communicate lung cancer risk and screening eligibility to low- and high-risk individuals?
- Role of risk prediction models in risk-based selection

**Risk-Based Screening Intervals**
- Current trial results and modelling favour annual screening
  - But risk-stratification by CT result can substantially reduce the screens needed:
    - Example: false positives, anxiety, overdiagnosis, radiation
  
  → E.g. results NELSON: probability of a lung cancer diagnosis in the two years following

- Negative baseline CT (no abnormality - no further risk)

  → Biennial screening for participants with negative baseline results? Need hard trial evidence

**European Lung Cancer Screening Implementation Trial**
**4-IN-THE-LUNG-RUN**

- the first large-scale multi-centered implementation trial on Volume CT lung cancer screening across 5 European countries
- to develop and implement the optimal personalized CT lung cancer screening programme for high-risk populations.
Study Design 4-IN-THE-LUNG-RUN

Co-morbidity reducing and smoking cessation services

- Due to the long-term smoking, screening eligible also prone to develop other major tobacco-related diseases as COPD and coronary artery diseases
  → Combined approach in the early detection and treatment of these diseases

- Personalized smoking cessation:
  - How to integrate information from the CT scan on tobacco-related comorbidities
  - Insufficient evidence: type of intervention, frequency, modality and content of the (health promoting) communication
  - Optimize use of teachable moments (CT-examination, results etc.)

Calcium scoring

Calcium scoring versus other risk factors

RESULTS CAC & smoking

RESULTS CAC & smoking
**ROBINSCA trial**

(Risk Or Benefit IN Screening for Cardiovascular disease)

Screening for cardiovascular disease risk using traditional risk factor assessment or coronary artery calcium scoring: the ROBINSCA trial

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**Home messages**

- Lung cancer is the leading cause of cancer-related mortality
- RCTs have confirmed substantial reductions in lung cancer mortality with low-dose computed tomography (LDCT) screening in high-risk populations
- The National Lung Screening Trial (NLST, n=53,454) and Dutch-Belgian Lung Cancer Screening trial (NELSON, n=9,792), 8.2% (men) and 25.6% (women)

---

**Gender Differences**

- Lung cancer mortality in NLST and NELSON
  - Men:
    - NLST: 0.92 (95% CI: 0.8–1.08)
    - NELSON: 0.76 (95% CI: 0.61–0.94)
    - LUSI: 0.94 (95% CI: 0.54–1.61)
  - Women:
    - NLST: 0.73 (95% CI: 0.6–0.9)
    - NELSON: 0.87 (95% CI: 0.81–1.4), 0.41-0.52 in earlier years (sign.)
    - LUSI: 0.34 (95% CI: 0.19–0.95)
  - Italian pooled analyses: 3.51 (95% CI: 1.50–9.21) for men as compared to women

---

**Step-“wise” implementation is NOW!**

Many of suggested cost-effective lung cancer screening scenarios will give more benefits than present cancer screening programmes

Disclaimer: limited information on non-Caucasian population & never-smokers

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www.lungca.or.kr
4-IN-THE-LUNG-RUN Consortium

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6Antwerp University Hospital, Belgium

Financial disclosure

4-IN-THE-LUNG-RUN is financially supported by the EU – Horizon 2020. https://cordis.europa.eu/project/id/680026

Participating countries 4-ITLR-trial so far

<table>
<thead>
<tr>
<th>Country</th>
<th>Number of screening sites</th>
<th>Planned number of pts per country</th>
<th>Planned number of screenings per week</th>
</tr>
</thead>
<tbody>
<tr>
<td>Netherlands</td>
<td>1</td>
<td>1,000</td>
<td>250</td>
</tr>
<tr>
<td>Germany</td>
<td>3</td>
<td>1,000 and 2,000</td>
<td>275</td>
</tr>
<tr>
<td>Spain</td>
<td>2</td>
<td>1,000</td>
<td>95</td>
</tr>
<tr>
<td>Turkey</td>
<td>1</td>
<td>2,500</td>
<td>130</td>
</tr>
<tr>
<td>Italy</td>
<td>3</td>
<td>2,000</td>
<td>50</td>
</tr>
<tr>
<td>Total Number of screening sites</td>
<td>21,620</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Norway</td>
<td>1</td>
<td>1,000</td>
<td>80</td>
</tr>
</tbody>
</table>

1 It is expected that a total of 2,000 participants will be enrolled in the countries receiving funding, and will be randomized to either screening intervention. All participants receiving funding planned to enrol at least 100 participants.
Plenary Session III.

Chair: Myung Ju Ahn (Korea)
Checkpoint inhibitors have revolutionized the first line therapy of stage IV non-small cell lung cancer, becoming part of standard therapy for all subsets of non-driver mutant tumors. Long term data are available now from the first trials showing a significant fraction of patients alive at 5 years, almost never seen in the chemotherapy alone era. We now have multiple positive phase III trials with different PD-1 pathway agents with or without 4 cycles of chemotherapy, and in combination with CTLA4 agents alone or in combination with 2 cycles of chemotherapy in this space. Unfortunately, all of these trials use a chemotherapy alone comparator, forcing clinicians to make cross-trial comparisons, personal comfort levels with particular agents, local reimbursement policies, and anecdotal personal experience to make the choice of regimens for a particular patient. Pharmaceutical companies do not seem inclined to perform head-to-head comparisons, even comparing combinations using only their agent such as whether chemotherapy improves outcomes with PD-L1 high disease, let alone directly comparing different agents and approaches to each other. We have become accustomed to pharma leading the way to answer the big questions in lung cancer but these are questions best answered in academic-led trials without a financial stake in the outcome. Fortunately these are starting to be considered, but still unfortunately require participation of pharmaceutical companies to provide off-label drug, a major hurdle.

In spite of our successes in improving long-term outcomes, less than half of patients respond to PD-1 pathway targeting and less than half of these become long-term survivors, so there is active investigation ongoing with novel immunotherapies and combinations that will hopefully inform improved standards of care in the future. In addition, after a decade of increasingly precise matching of patients to therapies with targeted agents, resulting in very high fractions of patients benefiting, we are regressing to a “one size fits all” approach to immunotherapy. It is very clear that there are multiple mechanisms of immune escape used by tumors and it makes no scientific sense to assume all tumors use only the PD-1 pathway. We are thus in desperate need of science-based approaches to in-
telligently select immunotherapy pathway targets and combination options for individual patients. It is hoped that intense molecular analysis of biospecimens from patients with response and non-response to candidate agents will provide these in the future.
Scientific Symposium II.
Clinical Genomics in Lung Cancer

Chair: Dong-Wan Kim (Korea)
Utilizing Machine Intelligence for Neoantigen Identification

Jung Kyoong Choi\textsuperscript{1,2}, Se-Hoon Lee\textsuperscript{3,4}

\textsuperscript{1}Department of Bioengineering, KAIST, Daejeon, \textsuperscript{2}PentaMedix Co., Ltd., Seongnam, \textsuperscript{3}Department of Medicine, Samsung Medical Center, Seoul, \textsuperscript{4}Department of Health Sciences and Technology, Sungkyunkwan University, Seoul, Korea

Neoantigen burden is regarded as a fundamental determinant of response to immunotherapy. However, its predictive value remains in question because some tumours with high neoantigen load show resistance. Here, we investigate our patient cohort together with a public cohort by our algorithms for the modelling of peptide-MHC binding and inter-cohort genomic prediction of therapeutic resistance. We first attempt to predict MHC-binding peptides at high accuracy with convolutional neural networks. Our prediction outperforms previous methods in > 70% of test cases. We then develop a classifier that can predict resistance from functional mutations. The predictive genes are involved in immune response and EGFR signalling, whereas their mutation patterns reflect positive selection. When integrated with our neoantigen profiling, these anti-immunogenic mutations reveal higher predictive power than known resistance factors. Our results suggest that the clinical benefit of immunotherapy can be determined by neoantigens that induce immunity and functional mutations that facilitate immune evasion.
Understanding tumor immune microenvironments is critical for identifying immune modifiers of cancer progression and developing cancer immunotherapies but it is increasingly evident that different cancer types may harbor distinct characteristics of subtypes, functional states and cell-cell interactions for tumor-infiltrating immune cells. We first performed deep single-cell RNA sequencing on thousands of single T cells isolated from peripheral blood, tumor and adjacent normal tissues from multiple cancer types including lung cancer. The transcriptional profiles of these individual cells, coupled with assembled TCR sequences, enabled us to identify T cell subsets based on their molecular and functional properties, and delineate their developmental trajectory. Although almost all subtypes of T cells can be found across different cancer indications, their relative abundance and functional states exhibit distinct and reproducible patterns, which might contribute, at least in part, to the differential clinical response rates to checkpoint blockade. Additionally, to examine the dynamic changes of tumor-infiltrating immune cells during cancer immunotherapy, we have started using single cell sequencing to track the dynamic changes of T cells post-treatment in lung cancer patients, and we will show the preliminary results. Such analyses provide opportunities for understanding the detailed characteristics of each of the detailed cell types as well as the identifying novel therapeutic targets for cancer immunotherapy.
Mutational processes giving rise to lung adenocarcinomas (LADCs) in non-smokers remain elusive. We analyzed 138 LADC whole genomes, including 83 cases with minimal contribution of smoking-associated mutational signature. Genomic rearrangements were not correlated with smoking-associated mutations and frequently served as driver events of smoking-signature-low LADCs. Complex genomic rearrangements, including chromothripsis and chromoplexy, generated 74% of known fusion oncogenes, including EML4-ALK, CD74-ROS1, and KIF5B-RET. Unlike other collateral rearrangements, these fusion-oncogene-associated rearrangements were frequently copy-number-balanced, representing a genomic signature of early oncogenesis. Analysis of mutation timing revealed that fusions and point mutations of canonical oncogenes were often acquired in the early decades of life. During a long latency, cancer-related genes were disrupted or amplified by complex rearrangements. The genomic landscape was different between subgroups—EGFR-mutant LADCs had frequent whole-genome duplications with p53 mutations, whereas fusion-oncogene-driven LADCs had frequent SETD2 mutations. Our study highlights LADC oncogenesis driven by endogenous mutational processes.
Genomic Heterogeneity of Advanced
EGFR-mutant Lung Cancer

Tae Min Kim
Department of Internal Medicine, Seoul National University Hospital, Seoul, Korea

EGFR-mutant lung cancer is a major molecular subtype of non-small cell lung cancer (NSCLC), representing approximately 60% of lung adenocarcinomas in Korea. The most common EGFR mutations are exon 19 in-frame deletion and L858R substitution, accounting for more than 80% of EGFR-activating mutations that are sensitive to EGFR tyrosine kinase inhibitors (TKIs). In addition, de novo and clonal $EGFR^{T790M}$ mutation is observed in about 1% of EGFR-mutant NSCLC. Furthermore, $EGFR$ exon 20 insertion mutations in the $\alpha$C-$\beta$4 loop are observed in approximately 4% of EGFR-mutant NSCLC. Recently, osimertinib, the 3rd-generation EGFR TKI has been approved as the first-line treatment for typical $EGFR$-mutant NSCLC (exon 19 deletion and L858R mutation). Although osimertinib improved survival outcomes, acquired resistance has been inevitable with heterogeneous mechanisms. Our experiences of cancer genome sequencing revealed novel mechanisms of EGFR TKI resistance in advanced EGFR-mutant lung cancer. Based on these experiences, whole genomic landscape of EGFR mutation-positive advanced non-small cell lung cancer treated with first-line osimertinib (WARRIOR) was initiated to identify acquired resistance mechanisms to osimertinib at whole-genome levels (NCT03969823).

References

Education Session VI.
Lung Cancer Screening

Chair: Jin Mo Goo (Korea)
Harms, Benefits and Cost-Effectiveness of Lung Cancer Screening

Harry J. de Koning
Department of Public Health, Erasmus MC, Rotterdam The Netherlands

- The step-wise decision-making concerning potential new cancer screening programmes include the establishment of evidence of effectiveness, benefits that outweigh the harms, and cost-effectiveness.

In: European Guide on Quality Improvement in Comprehensive Cancer Care (2013) by T. Alletti, A. Bobrowska & M. van der Burde
# Reduced Lung-Cancer Mortality with Volume CT Screening in a Randomized Trial

**Original Article**


## NELSON trial

13,792 people voluntarily participated in the study. 65% of these participants are male.

The participants were randomly assigned to one of the study groups:
- **Screening group**: 328 participants receive a series of CT scans
- **Control group**: 328 participants do not receive a CT scan (usual care)

The participants in the screening group received four CT scans, with increasing intervals.

## Stage Shift NELSON males

- | Screening group (341 lung cancers found) | Control group (104 lung cancers found) |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>I (60%)</td>
<td>III (18%)</td>
</tr>
<tr>
<td>II (18%)</td>
<td>II (18%)</td>
</tr>
<tr>
<td>III (18%)</td>
<td>I (18%)</td>
</tr>
</tbody>
</table>

- 203 of these cancers were detected by CT scans of the NELSON study in the first 5.5 years.

## Cause of Death in Male Participants NELSON

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (n=341)</th>
<th>Screening Group (n=341)</th>
<th>Control Group (n=104)</th>
<th>Rate Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cause of death</td>
<td>284 (83%)</td>
<td>269 (80%)</td>
<td>15 (14%)</td>
<td>0.57 (0.38-0.86)</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>148 (44%)</td>
<td>130 (38%)</td>
<td>18 (17%)</td>
<td>0.54 (0.32-0.91)</td>
</tr>
<tr>
<td>Other cancers</td>
<td>36 (10%)</td>
<td>33 (9%)</td>
<td>3 (3%)</td>
<td>1.06 (0.48-2.35)</td>
</tr>
<tr>
<td>Non-small cell lung cancer</td>
<td>132 (39%)</td>
<td>117 (34%)</td>
<td>15 (14%)</td>
<td>0.77 (0.45-1.32)</td>
</tr>
<tr>
<td>Small cell lung cancer</td>
<td>15 (4%)</td>
<td>12 (3%)</td>
<td>3 (3%)</td>
<td>1.00 (0.33-3.20)</td>
</tr>
<tr>
<td>Other cancers</td>
<td>23 (6%)</td>
<td>20 (6%)</td>
<td>3 (3%)</td>
<td>1.00 (0.33-3.20)</td>
</tr>
<tr>
<td>Cause of death—other</td>
<td>136 (39%)</td>
<td>118 (36%)</td>
<td>18 (17%)</td>
<td>0.88 (0.57-1.37)</td>
</tr>
</tbody>
</table>

Plzen: 23-12-2008 – 08-07-2009

K: 20-10-2008 – 31-10-2010

Page 144 of the Korean Association for Lung Cancer
• At present, the high referral rates seen in the US do not seem feasible in Europe, and mortality results are therefore needed from the European trials with lower referral rates.

In: European Guide on Quality Assurance in Comprehensive Cancer Control (2011) by F. Abraham, M. Raskova & M. van den Bosse

Screening Test Results in Male Participants

Table 1. Screening Test Results in Each Screening Round for Male Participants in the Screening Group

<table>
<thead>
<tr>
<th>Round</th>
<th>Screened Number</th>
<th>Undetected Number</th>
<th>Estimated Misdiagnosis Rate</th>
<th>Estimated Missed Cancer Rate</th>
<th>Positive Cancer Rate</th>
<th>Positive Predictive Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Round 1</td>
<td>6233/6301 (98.6)</td>
<td>324/6301 (5.1)</td>
<td>47/324 (14.4)</td>
<td>14/324 (4.3)</td>
<td>16/6301 (0.2)</td>
<td>30.2</td>
</tr>
<tr>
<td>Round 2</td>
<td>6084/6095 (99.8)</td>
<td>304/6095 (4.9)</td>
<td>57/304 (18.7)</td>
<td>15/304 (4.9)</td>
<td>48/6095 (0.8)</td>
<td>47.4</td>
</tr>
<tr>
<td>Round 3</td>
<td>5780/5798 (99.8)</td>
<td>232/5798 (4.0)</td>
<td>40/232 (17.2)</td>
<td>13/232 (5.6)</td>
<td>25/5798 (0.4)</td>
<td>45.1</td>
</tr>
<tr>
<td>Round 4</td>
<td>4021/4026 (99.9)</td>
<td>86/4026 (2.1)</td>
<td>17/86 (19.5)</td>
<td>12/86 (14.3)</td>
<td>37/4026 (0.9)</td>
<td>41.6</td>
</tr>
<tr>
<td>Total</td>
<td>22,680/23,086 (98.3)</td>
<td>1,095/23,086 (4.7)</td>
<td>228/1,095 (20.9)</td>
<td>70/1,095 (6.4)</td>
<td>541/23,086 (2.3)</td>
<td>45.5</td>
</tr>
</tbody>
</table>

Message indeterminates screening test result:
“Please have observed a very small abnormality in your lung (5–6 mm long). Such a small abnormality is often detected in many patients and is usually a small scar or a minor deformation. Therefore, at this moment, there is no need for any further investigations. However, in order to see whether there has been any change in this abnormality, a new CT scan of the lung will be made after 2 to 4 months.”
WHAT NEXT

- For lung cancer screening, the evidence on effectiveness, benefits that outweigh the harms, and cost-effectiveness, is now firm.
- Once evidence exists to support these criteria, implementation research in each country is needed to assess the feasibility of fulfilling the national requirements in practice.

Capacity challenge

Cost-effectiveness & efficient frontier

Number of scenarios considered

ten Haaf et al. PLOS Medicine, 2017
**Costs**

- Program related costs:
  - Costs for inviting individuals
  - Costs for risk assessment(s)
  - Costs of the screening test and follow-up examinations
  - Costs for maintaining the program (IT infrastructure etc.)

- Treatment related costs:
  - Shift in treatment (costs) from advanced cancers to less advanced cancers
  - Long-term care costs for persons who now survive cancer
  - Cancer care costs that would not have occurred without screening (due to overdiagnosis)

**Discussion & conclusion**

- Newest more favorable results NELSON not yet incorporated
- Conservative estimates cost of screening (unit cost 250+)
- Cost savings: immunotherapies not yet included
- Cost savings after negative baseline CT possible? (4-ITLRun trial)

- Absolute benefits can be substantially higher than present other cancer screening programmes

- We have to be selective in eligibility, but CT lung cancer screening can be a cost-effective preventive health care scen
NL prediction using NELSON Dutch demographic data (but effectiveness NLST) – 17 million population

<table>
<thead>
<tr>
<th>Age group</th>
<th>Eligible</th>
<th>CT scans per year</th>
<th>LC deaths prevented (ytd)</th>
</tr>
</thead>
<tbody>
<tr>
<td>55-69 yrs</td>
<td>1,300,000</td>
<td>400,000</td>
<td>2,700</td>
</tr>
<tr>
<td>70-74 yrs</td>
<td>800,000</td>
<td>600,000</td>
<td>1,900</td>
</tr>
<tr>
<td>75-79 yrs</td>
<td>600,000</td>
<td>400,000</td>
<td>3,100</td>
</tr>
</tbody>
</table>

Lung Cancer Screening

- Screening eligibility based on risk assessment, so that not everyone in a certain age group is offered screening.
- Two main selection methods:
  - USPSTF (Age 55-80, ≥20 pack-years, smoked within 15 years)
  - Risk prediction tools such as PLCO (62% non-smoking and 40% smoking predictors)

Risk-Based Eligibility

- Prevent screening of the low-risk (but anxious?) population
  - Example: PLCO (62% vs 1.6% risk threshold yields a similar number of LYG as the USPSTF criteria, but requires 50% less CT scans)
- Risk-based strategies more likely to recruit older individuals and groups with diminished life-expectancies
  - More research needed to identify the optimal thresholds for risk-based selection
- How do we communicate lung cancer risk and screening eligibility to low- and high-risk individuals?
- Role of risk prediction models in risk-based selection

Risk-Based Screening Intervals

- Current trial results and modelling favor annual screening
- But risk stratification by CT result can substantially reduce the screens needed:
  - Harms (e.g. false positives, anxiety, overdiagnosis, radiation)
  - Gains
- E.g. results NELSON: probability of a lung cancer diagnosis in the two years following:
  - Negative baseline CT
  - Positive (or uncertain) baseline CT
  - 25.7
- Biennial screening for participants with negative baseline results? Need hard trial evidence

European Lung Cancer Screening Implementation Trial

4-IN-THE-LUNG-RUN

- the first large-scale multi-centered implementation trial on Volume CT lung cancer screening across 5 European countries
- to develop and implement the optimal personalized CT lung cancer screening programme for high-risk populations.
To assess the relative safety (i.e., comparable detection of favourable lung cancer stages I-II) of a personalized risk-based (often) less intensive screening regimen on the basis of a combination of (a) health risk factors, (b) baseline CT scan result and possibly ultimately (c) biomarker outcomes amongst individuals aged 60-79 years at high risk for developing lung cancer.

24,000 individuals with a baseline negative screening test result, who have given consent, will be randomised (1:1) to personalised screening (initially biennially) or standard screening (annually).

- 4 men and women, aged 60-70 years, with a PLOD<sub>16</sub> 6-year risk for developing lung cancer of 3.25% or a smoking history of 140 pack-years, being a current smoker or former smoker who quit smoking ≥10 years ago.

**RESULTS CAC & smoking**

<table>
<thead>
<tr>
<th>Odds ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plan</td>
<td></td>
</tr>
<tr>
<td>Age, per 10 years</td>
<td>0.001***</td>
</tr>
<tr>
<td>Educational level</td>
<td>0.049*</td>
</tr>
<tr>
<td>Low</td>
<td>0.018</td>
</tr>
<tr>
<td>Medium</td>
<td>0.048</td>
</tr>
<tr>
<td>High</td>
<td>0.039</td>
</tr>
<tr>
<td>Body Mass Index cut-off</td>
<td>0.004***</td>
</tr>
<tr>
<td>Family history of CVD</td>
<td>0.004***</td>
</tr>
<tr>
<td>Smoker at baseline</td>
<td>0.005***</td>
</tr>
<tr>
<td>Orlistat</td>
<td>0.001***</td>
</tr>
<tr>
<td>Atherosclerosis in past year</td>
<td>0.001***</td>
</tr>
<tr>
<td>Antihypertensive medication</td>
<td>0.001***</td>
</tr>
<tr>
<td>Lipid-lowering medication</td>
<td>0.026</td>
</tr>
</tbody>
</table>

Area under the curve: 0.699

**Home messages**

- Lung cancer is the leading cause of cancer-related mortality
- RCTs have confirmed substantial reductions in lung cancer mortality with low-dose computed tomography (LDCT) screening in high-risk populations
- The National Lung Screening Trial (NLST, n=53,454) and Dutch-Belgian Lung Cancer Screening trial (NELSON, n=15,792), 8-24% (men) and 26-61% (women)

**Personalized Risk-Based Screening**

<table>
<thead>
<tr>
<th>Individually tailored interventions</th>
<th>Individually risk-based interventions</th>
<th>Individually screening strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Personalized Risk-Based Lung Cancer Screening</td>
<td>Personalized Risk-Based Lung Cancer Screening</td>
<td>Personalized Risk-Based Lung Cancer Screening</td>
</tr>
<tr>
<td>Individualised treatment</td>
<td>Individualised treatment</td>
<td>Individualised treatment</td>
</tr>
<tr>
<td>Individualised intervention</td>
<td>Individualised intervention</td>
<td>Individualised intervention</td>
</tr>
<tr>
<td>Health promotion</td>
<td>Health promotion</td>
<td>Health promotion</td>
</tr>
<tr>
<td>Prevention of smoking</td>
<td>Prevention of smoking</td>
<td>Prevention of smoking</td>
</tr>
<tr>
<td>Smoking cessation</td>
<td>Smoking cessation</td>
<td>Smoking cessation</td>
</tr>
<tr>
<td>Personalised treatments</td>
<td>Personalised treatments</td>
<td>Personalised treatments</td>
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<tr>
<td>Optimisation of treatment</td>
<td>Optimisation of treatment</td>
<td>Optimisation of treatment</td>
</tr>
<tr>
<td>Optimisation of patient outcomes</td>
<td>Optimisation of patient outcomes</td>
<td>Optimisation of patient outcomes</td>
</tr>
</tbody>
</table>

**Nelson's impact**

Many of suggested cost-effective lung cancer screening scenarios will give more benefits than present cancer screening programmes.
Low-dose computed tomography (LDCT) is effective for lung cancer screening and can reduce lung cancer mortality. However, most of the LDCT screenings focused on heavy smoker which were not suitable for East Asian population. In Taiwan, lung cancer is the leading cause of cancer mortality and 53% were never-smoker. We conducted a nationwide lung cancer LDCT screening on never-smoker (TALENT: Taiwan Lung Cancer Screening for Never Smoker Trial) aiming to develop an effective strategy to identify subjects with high risk for LDCT screening of lung cancer in never-smoker. The TALENT study is a prospective, multicenter study sponsored by The Ministry of Health and Welfare, Taiwan. The inclusion criteria were age between 55-75 years, never-smoker and having one of the following risks: family history of lung cancer within third-degree, passive smoking exposure, TB/COPD, cooking index ≥ 110, and not using ventilator during cooking. A solid or part-solid (PS) nodule larger than 6 mm or pure ground glass nodule (GGN) larger than 5 mm in diameter was designated as positive on LDCT. From Feb. 2015 to July 2019, a total of 12,011 subjects were enrolled. Among them, 6,012 (50.1%) had lung cancer family history, 5,999 (49.9%) did not. In 12,011 scans, 2,094 (17.4%) were considered positive, there were 392 subjects (3.3%) underwent lung biopsies or surgeries at T0, lung cancer (2.6%) were diagnosed in 311 subjects, 254 (2.1%) were invasive lung cancer. All but one was adenocarcinoma and 96.5% were stage 0 or I, 81 had benign lung disease or malignancy other than primary lung cancer. The prevalence of lung cancer was 3.2% and 2.0% in subjects with and without lung cancer family history, respectively. The TALENT study confirmed the effectiveness of LDCT screening in a pre-defined, never-smoker high-risk population. The T0 lung cancer detection rate was 2.6%, which was even higher than NLST study (1.1%) and NELSON study (0.9%). Most of the patients (96.5%) were stage 0 or 1 and potentially curable by surgery. Subjects with family history may have higher risk of lung cancer in never smoker.
Lung cancer screening with low-dose CT (LDCT) has shown to reduce lung cancer mortality in several randomized clinical trials. Most nodule management systems are based on the nodule type (solid, part-solid, nonsolid) and nodule size. Traditionally the nodule size was measured manually and expressed as one-dimensional diameter or two-dimensional average diameter. Recently, many studies have shown the value of nodule volumetry obtained with software in reducing interobserver variability and predicting nodule malignancy. Calculating the volume doubling time can be used in this process. In addition to the assessment of lung nodule, LDCT provides valuable information on smoking-related diseases such as emphysema and coronary artery disease. Management based on this information can contribute to reducing all-cause mortality. With the advance of machine learning techniques, quantitative analysis of LDCT in lung cancer screening will be more effectively explored.
Liquid Biomarkers in Lung Cancer Screening

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LDCT screening of high-risk patients has been demonstrated to reduce lung cancer mortality, but high false-positive rate and subsequent unnecessary invasive interventions can be harmful for the patients. LDCT based protocol, largely based on nodule size and/or volume, has the advantage of the simplicity and the sensitivity, but fundamentally imaging is not sufficient for successful screening. There are huge unmet needs for evidence-based liquid biomarkers to support LDCT screening. Lung cancer screening is performed with two steps composed of nodule detection by LDCT and subsequent confirmation of malignancy. Usually most nodules detected on annual screening are often so small that they are out of reach of current biopsy techniques. Ground glass nodules (GGNs) are hardly accessible for tissue biopsy and the matter of multiple, even bilateral, nodules are often confronted. Extensive researches are undergoing to discover lung cancer screening liquid biomarkers. Blood is an obvious first choice due to its easy accessibility and repeatability, but the sensitivity is not enough to detect early lung cancer. Urine and saliva are potential sources of biomarkers. Sputum and exhaled breath condensates (ECB) are more specific samples reflecting the molecular and genetic changes of respiratory tract, but the sensitivity is still limited. Bronchoalveolar lavage fluid (BALF) may be the most relevant sample due to its direct accessibility to tumor cells and microenvironment. There are four major liquid biosources in cancer; circulating tumor cells (CTCs), circulating tumor DNA (ctDNA), extracellular vesicles (EVs), and tumor-educated platelets (TEPs). Liquid biopsy using ctDNA is the most commonly used owing to repeatability and non-invasiveness, but low sensitivity due to the matter of its DNA instability and short half-life may be an important limiting factor, while EVs make an ideal cancer biomarker as the contents of EVs from tumor cells reflect molecular and genetic composition of parental cells and are secreted in higher abundance compared to EVs of normal cells. Using these liquid biosources, almost all kinds of molecular and genetic investigations are ongoing including genetic, genomic, epigenetic, proteomic and metabolomic methodologies. Ongoing or planned trials to show clinical utility of liquid biomarkers in the context of lung cancer screening will be introduced and reviewed.
Satellite Symposium IV.
AstraZeneca

Chair: Kye Young Lee (Korea)
Is it time for a Paradigm Shift in first Line Treatment of Advanced NSCLC?

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The treatment landscape of non-small cell lung cancer (NSCLC) are rapidly evolving. Especially, lung cancer with EGFR mutation and locally advanced stage III NSCLC have made remarkable progress in treatment strategies. Herein, I’d like to focus on the osimertinib in EGFR mutant lung cancer and durvalumab in unresectable stage III NSCLC as upfront treatment.

Osimertinib is a third-generation, irreversible tyrosine kinase inhibitor (TKI) of the EGFR that selectively inhibits both EGFR-TKI-sensitizing and EGFR T790M resistance mutations. A phase 3 trial compared first-line osimertinib with other EGFR-TKIs in patients with EGFR mutant advanced NSCLC (FLAURA). The trial showed longer PFS with osimertinib than with the comparator EGFR-TKIs (hazard ratio for disease progression or death, 0.46). FLAURA demonstrated a statistically significant improvement in OS in the patients randomized to osimertinib compared to standard of care. In the FLAURA China study, median OS was extended by a clinically meaningful 7.4 months in the osimertinib group vs comparator EGFR TKI group.

These results were consistent with the global population, where median OS was extended by 6.8 months in the osimertinib group.

In the phase 3 PACIFIC study of patients with unresectable stage III NSCLC without progression after chemoradiotherapy, durvalumab demonstrated significant improvements versus placebo in the primary end points of progression-free survival (HR = 0.52, p < 0.0001) and overall survival (OS) (HR = 0.68, 3–0.87, p = 0.00251), with manageable safety and no detrimental effect on patient-reported outcomes. Durvalumab after chemoradiotherapy in Stage III NSCLC: 4-year survival update from the Phase 3 PACIFIC trial was reported in this ESMO. The median OS for the Imfinzi arm was reached for the first time at this update. Imfinzi mOS = 47.5 months; placebo mOS = 29.1 months. HR 0.71. The PACIFIC regimen continues to demonstrate durable PFS and sustained OS benefit at 4 years.
Education Session VII.
Management of Brain Metastases

Chair: Si Yeol Song (Korea)
This presentation will provide a comprehensive review of preclinical and clinical evidence in support of the thesis that hippocampal neural stem cell irradiation causes cognitive toxicity. This review will include detailed discussion of practice-changing evidence from NRG CC001, a phase III trial of hippocampal-avoidant whole-brain radiotherapy versus conventional whole-brain radiotherapy for patients with brain metastases, and how this evidence influences modern management of brain metastases. In addition, ongoing and future brain metastasis trials will be presented.
Nowadays, multidisciplinary approach is tailored for each individual patient with brain metastases among the various therapeutic modalities. Although stereotactic radiosurgery (SRS) or whole brain radiation therapy (WBRT) is the preferred primary treatment for a greater part of the patients, surgical treatment has provided beneficial effects in the selected subgroup. In the early 1990s, two independent randomized prospective trials demonstrated a survival benefit resulting from the addition of resection to WBRT in the treatment of single brain metastasis. In addition to survival prolongation, surgical resection provides rapid relief of the intracranial mass effect, thereby improving neurological condition of the patients, and lowering steroid dependency. Also, diagnostic information can be obtained in cases with unknown primary histological type or with suspicion of radiation necrosis.

Traditionally, a surgically accessible single lesion larger than 3 cm in diameter has been regarded as an ideal surgical indication. With recent development of surgical techniques and imaging modalities, the patients with limited number of brain metastases may benefit from surgical resection along with postoperative SRS or adjuvant WBRT. However, surgical morbidity, especially systemic complications such as pneumonia or deep vein thrombosis are not rare, and surgical mortality has been reported to be up to 4 percent. Therefore, proper selection of the surgical candidates is essential. To minimize postoperative complications, the clinical and functional status of the patient should be considered whether the patient is medically suitable for both surgery and recovery. Also, the status of systemic disease should be carefully considered whether the patient can benefit from local central nervous system tumor control.

In summary, surgical treatment should be considered and recommended with SRS or WBRT to patients with good functional status, expected reasonable systemic cancer control, limited number of lesions which are harboring mass effect and surgically accessible, so as to prolong survival and improve the quality of life.
Brain is a sanctuary organ, and is often intractable when it comes to metastasis management. Brain metastases are present in 26% of patients with stage 4, non-small cell lung cancer (NSCLC) at presentation. Brain metastases are significantly associated with patient morbidity and mortality. Leptomeningeal disease is rarer, and associated with worse prognosis.

So far, much of the data on brain treatment is retrospective. Clinical trials of systemic treatments largely exclude patients with brain metastases. Recently development of next-generation targeted therapy in patients with driver mutations (EGFR, ALK and ROS1) have impressive central nervous system (CNS) penetrance and response rates. Unfortunately, no prospective data can currently guide the timings or modality of local therapies with systemic treatments in these patients who have a high incidence of CNS disease. Recent immunotherapy trials have included patients with brain metastases. These patients have largely been pre-treated with local therapies and are asymptomatic. Pooled analyses of patients with brain metastases showed that PD-L1-positive NSCLC patients derived clinical benefit irrespective of the presence of brain metastases at baseline. In the future, prospective studies are needed in patients with brain metastases to guide optimal treatment options, balancing between both systemic and local treatment.
For the optimal treatment selection of brain metastases (BMs), both the BMs’ status and the patient’s prognosis should be taken into account. The goals of cancer treatment are to save the patient’s life and maintain or improve his or her quality of life by controlling the tumor(s), and the same is true for patients with BMs. The control of BMs is particularly crucial when the BMs are symptomatic and/or life-threatening. The current trend of treatment for single to oligo-BMs is stereotactic radiosurgery (SRS) alone, administering a high dose in a single session. The omission of upfront whole brain radiation therapy (WBRT) is becoming the mainstream for the purpose of avoiding radiation-induced cognitive decline. In addition, with the latest technology, it has become possible to treat up to 10 lesions within 30 min by using single-isocenter volumetric arc therapy. However, SRS monotherapy has some weaknesses, one is its limited therapeutic effect on large (>2.0 cm) tumors. Hypofractionated stereotactic radiotherapy (HSRT) can be a solution for this limitation to some extent. Another drawback of SRS monotherapy is the high risk of brain tumor recurrence at distant sites in the brain including leptomeningeal dissemination. The use of WBRT in combination with SRS reduces the intracranial tumor progression, but the use of ‘standard-dose’ WBRT increases the risk of neurocognitive deterioration resulting from radiation sequelae. Hippocampal avoidance-WBRT (HA-WBRT) or the use of memantine could help reduce the degree of neurocognitive deterioration. I have been investigating reduced-dose WBRT (25 Gy in 10 fractions) for patients indicated for SRS or HSRT, with the aim of reducing the degree of neurocognitive deterioration without compromising the brain tumor control, in the JROSG13-1 trial. The final results of this trial will be presented soon. Patient selection is also important for determining the intensity of brain treatment in order to avoid over- as well as under-treatment. A second analysis of the JROSG 99-1 trial’s data (SRS vs. SRS+WBRT for up to four BMs) showed that improved brain tumor control could translate to improved survival for non-small cell lung cancer (NSCLC) patients with good prognoses. This finding is supported by the secondary analysis of the RTOG9508 trial’s data (WBRT vs. SRS+WBRT). It can thus now be hypothesized that the treatment intensity should be modified according to the patient’s prognosis as well as the size and/or number of BMs. Many issues remain to be investigated in prospective trials toward the creation of an algorithm for the optimal treatment selection for every patient with BMs.
Education Session VIII.
Immune Checkpoint Blockades in Lung Cancer

Chair: Jae Cheol Lee (Korea)
Predictive Biomarkers for Efficacy of Immune Checkpoint Blockades in Lung Cancer

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Checkpoint inhibitors have revolutionized the therapy of all subtypes of lung cancer, and have become the standard of care for both stage III and IV non-small lung cancer and extensive stage small cell lung cancer, as well as now mesothelioma. In spite of our successes in improving long-term outcomes, Most patients don’t respond to PD-1 pathway targeting and most tumors that respond ultimately relapse, so there is active investigation ongoing with novel immunotherapies and combinations that will hopefully inform improved standards of care in the future. Both targeted therapies and checkpoint inhibitors were discovered and developed based on solid basic scientific discoveries about the nature of cancer and its interaction with the host, but, after more than a decade of improved outcomes by increasingly precise matching of patients to therapies with targeted agents, we are regressing to a “one size fits all” approach to immunotherapy in which every patient gets the same therapy. The immune system is complex and it makes no scientific sense to assume all tumors use the PD-1 pathway alone to escape immune recognition. We are thus in desperate need of science-based approaches to intelligently select immunotherapy pathway targets and combination options for individual patients, beyond PD-L1 and TMB. Both PD-L1 and TMB influence the likelihood of response in many situations to a variable degree and only in certain situations. This fact, along with limited proven alternatives for targeting other pathways has led to the limited use of IO biomarkers in routine clinical practice today. It is hoped that novel immune pathway targets, improved basic science of immune escape, and intense molecular analysis of biospecimens from tumors exhibiting response or non-response to established and novel candidate agents will provide the scientific basis for rational selection of patients for specific therapies in the future.
Biomarker Research about Gene Testing in Immunotherapy

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Targeting of the immune system has been found to confer clinical benefit for patients with several types of advanced solid tumor, including non-small cell lung cancer (NSCLC). Currently approved immune checkpoint blockers are monoclonal antibodies that target the cytotoxic T lymphocyte-associated protein 4 (CTLA-4) or programmed cell death protein 1 (PD-1) pathways. Such immune-check point inhibition therapies demonstrated the definite survival benefit with only a limited number of patients experience a durable response in the salvage setting with no selective biomarker. Hence, the identification of individuals who are most likely to benefit from anti-PD-1 immunotherapy is an important clinical goal. Expression of PD-L1 in tumor tissue is the most well-established biomarker for treatment with antibodies to PD-1 or to PD-L1 in patients with advanced NSCLC. However, the identification of additional biomarkers is important because of the heterogeneity of the tPD-L1 and the clinical response to immune-checkpoint inhibitors (ICIs), which is likely due in part to the difficulty in defining PD-L1 positivity and limited assay standardization. Thus, based on the complex interactions between tumors and the immune microenvironments, multiple biomarkers are necessary to select responders.

Tumor mutation burden (TMB) is the second most common recognized biomarker for immunotherapy. We have evaluated TMB for patients with EGFR mutations and found that patients with high TMB might be appropriate candidate to receive immune-checkpoint inhibitors. Moreover, the development of gene expression profiling of tumors has enabled to identify gene expression signatures and patient selection with molecular targeted therapies. Recent study including us have evaluated the association of immune-related gene expression in patients treated with immunotherapy. Here, previous and current our findings by translational research using tumor specimens will be presented here.
The immune checkpoint inhibitor (ICI) has been strongly positioned as a valuable treatment modality for advanced or metastatic non-small cell lung cancer (NSCLC). As ICIs commonly used in the clinical practice, two unique phenomena, pseudoprogression and hyperprogression, are not infrequently seen, which are least recognized in cytotoxic chemotherapy or target therapy.

Pseudoprogression is defined as initial tumor progression subsequently followed by spontaneous tumor shrinkage, and it was first reported in melanoma studies. The incidence of pseudoprogression in NSCLC has been reported variously as 0.6 – 5.8%. If initial tumor progression before tumor shrinkage is defined as any increase of tumor size not as “progressive disease” by RECIST, the incidence can be increased. In addition, the incidence could be underestimated because many patients who experienced tumor progression are hard to continue immunotherapy because of many reasons in clinical practice. Considering pseudoprogression of immunotherapy, immune-related response criteria (irRC) was introduced in tumor response evaluation in 2009. The newly adopted evaluation criteria in irRC, such as the confirmation of progressive disease required after one month from the first appearance of progressive disease and new lesions only cannot be directly interpreted as “progressive disease”, is short to completely differentiate pseudoprogression from true disease progression. The most important point in differentiating two phenomena is the change in patients’ performance status or tumor related symptoms. Since the underlying mechanism of pseudoprogression is in part immune cell infiltration to tumor, so that it does not cause the deterioration of patients’ performance status or symptoms.

Hyperprogression indicates the phenomenon of dramatic tumor increase which outpaces the expected rate. Its incidence is more variously reported than pseudoprogression from 4 to 29% in NSCLC patients. The wide range in incidence rates are caused by the nature of retrospective studies and different definition of hyperprogression in the studies. In addition, unlike pseudoprogression, the underlying mechanism of hyperprogression is poorly evaluated. The hyperprogression received the spotlight at first as many prospective studies comparing ICIs with chemotherapy.
showed inferior survival outcomes of ICIs in the first few months compared with chemotherapy. Based on these phenomena, some physicians have thought ICIs themselves promote or aggravate tumor cell proliferations. However, in the phase 3 studies comparing nivolumab with placebo in gastric cancer patients, the early drops in survival curve are similar between two arms (nivolumab vs placebo). This study suggests the ICIs, at least, do not promote tumor cell proliferation. In addition, the OAK study in NSCLC, the proportions of fast-progressors were similar (10%) between two arms, atezolizumab and docetaxel arms.

In addition to no definite underlying mechanism of hyperprogression, the fact that no predictive factor for hyperprogression has been documented makes us hard to manage or prepare for it. The most promising predictive factor, STK11 mutation, was related with poor outcomes for ICIs in several retrospective trials. However, it was found to be more likely prognostic factor than predictive factor in an explorative analysis of KEYNOTE 042.

Based on the data reported until now, the hyperprogression exists in ICI therapy era, though its incidence is not as high as reported in many retrospective trials. Until now, however, there are no data or underlying mechanism, with which ICIs themselves promote rapid proliferation of tumor cells. Therefore, hyperprogression could be a clinical phenomenon of natural course of tumor progression, in which tumor cell proliferation is disinhibited after being suppressed by prior cytotoxic chemotherapy or target therapy.

We should keep in mind that hyperprogression can develop when we treat patients with ICIs, and the switch from ICIs to chemotherapy is urgently needed in the situation. Another strategy for preparation of the possible hyperprogression is the combined chemotherapy with immunotherapy (chemoimmunotherapy), where early drop in survival curves was successfully prevented in some clinical trials, such as KEYNOTE 189 and CheckMate 9LA.
Immunotherapy has revolutionized the landscape of cancer treatment and become a standard pillar of the treatment of lung cancer. However, despite the striking clinical improvements, most patients suffer from disease progression or immunotherapy fails due to the evolution of primary or acquired resistance. Disappointingly, success of immune checkpoint inhibitors (ICIs) is limited to anti-programmed cell death protein-1/programmed cell death protein ligand-1 (PD-1/PD-L1) antibodies despite more successes follow in different clinical situations including adjuvant therapy after surgery, consolidation therapy after chemoradiotherapy and even in neo-adjuvant therapy before surgery. In addition, the success does not always repeat in all patients or disappears during the treatment. To overcome either primary or secondary resistance, therapeutic strategies adopt the combination of an ICI with chemotherapy or novel agents as first-line therapy or addition of novel agents to an ICI after failure of ICI therapy or switching to new combinations. Today, I will review mechanisms of the resistance and related biomarkers proposed to date and then introduce combination treatment strategies to overcome the resistance.
Oral Presentation III.

Chair: Tae Won Jang (Korea)
ANALYSIS OF DOSIMETRIC FACTORS ASSOCIATED WITH RADIATION PNEUMONITIS IN PATIENTS WITH NON-SMALL-CELL LUNG CANCER TREATED WITH CONCURRENT CHEMORADIOThERAPY FOLLOWED BY IMMUNOTHERAPY

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With recent advances in immunotherapy (IT), it has been applied to many patients with non-small-cell lung cancer (NSCLC). However, there are few studies of toxicity in patients receiving IT after concurrent chemoradiotherapy (CCRT). Therefore, we performed retrospective study to find out dosimetric factors that would predict radiation pneumonitis (RP) in these patients.

In total, 106 patients with unresectable NSCLC who underwent definitive CCRT between May 2018 and May 2020 were included. Dosimetric parameters evaluated were size of planning target volume (PTV), mean lung dose (MLD), and the percentage of lung volume receiving more than a threshold radiation dose (Vdose). The primary endpoint was the occurrence of radiation pneumonitis ≥ grade 2, and toxicity was evaluated based on CTCAE version 5.0.

51 out of 106 patients were treated with immune checkpoint blockade after CCRT. The median follow-up period from the end of radiotherapy was 11.5 months (range, 3.0-28.2). RP ≥ grade 2 occurred in 47 (44.3%), 27 in whom underwent immunotherapy (IT group) and in 20 without immunotherapy (Non-IT group). Median freedom from RP was significantly shorter in the IT group (IT group, 7.4 months; Non-IT group, Not reached) (p=0.041).

Median PTV size, MLD, V5, V10, V20, V30, V40 values were 317.6 cm³, 13.11 Gy, 45.8%, 33.2%, 22.3%, 16.3%, and 12.3%, respectively, and the mean value of those factors were not differ between two groups. Four dosimetric variables (MLD, V20, V30, and V40) had prognostic significance on univariate analysis for occurrence of pneumonitis (Dosimetric factor, Odds ratio, p-value; MLD, 3.0, 0.026; V20, 4.1, 0.001; V30, 3.1, 0.006; V40, 3.7, 0.002).

On subgroup analysis, only V20 was found to be significant risk factor in the Non-IT group and V30 and V40 in the IT group. In addition, when analyzing freedom from RP by the cutoff values of V30 and V40, it has been shown that toxicity was significantly increased in patients with high Vdose only within the IT group (p=0.01, 0.022).

Patients who received CCRT followed by IT were found to have an increased probability of developing RP due to the additive effect, which seems to be particularly related to the lung volume irradiated with high doses of radiation. Therefore, considering the extended application of IT in the future, several dosimetric factors, including high Vdose, must be carefully considered in treatment planning for NSCLC patients.

Keywords: Non-small-cell lung cancer, Concurrent chemoradiotherapy, Immunotherapy, Radiation pneumonitis, Dosimetric factor
PROTON THERAPY REDUCED THE LIKELIHOOD OF SEVERE RADIATION-INDUCED LYMPHOPENIA IN LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER: COMPARATIVE STUDY OF PROTON VS PHOTON

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In the era of immunotherapy, the interest in radiation-induced lymphopenia is increasing. We investigated differences in severe radiation-induced lymphopenia (SRL) after pencil-beam scanning proton therapy (PBSPT) or intensity-modulated (photon) radiotherapy (IMRT) for patients with locally advanced non-small cell lung cancer (NSCLC).

We retrospectively reviewed 213 patients who received definitive concurrent chemoradiotherapy with PBSPT (n=24) or IMRT (n=189). SRL was defined when two or more events of absolute lymphocyte counts (ALC) <200 cells/μL were observed in weekly laboratory test during chemoradiotherapy. Radiation dose-volume indices of normal organs were calculated. Stepwise-multivariate logistic regression with 10-fold cross-validation was performed to identify predictive values of SRL. Furthermore, 1:2 propensity-score matching (PSM) was performed between PBSPT and IMRT.

Baseline ALC was comparable between PBSPT and IMRT patients (median, 1,960 vs. 2,050 cells/μL; P=0.362). Lung volumes receiving 5–20GyE or higher and mean dose were significantly lower in PBSPT patients (all P<0.001). In both groups, ALC declined steadily during RT; SRL was frequently observed after IMRT than PBSPT (34.9% vs. 12.5%; P=0.027). With a median follow-up of 21.9 months, the 2-year overall survival of patients with SRL (N=69) was lower than that of patients without SRL (N=144) (69.1% vs. 79.9%; P=0.026); SRL was significantly associated with inferior survival in multivariable analysis (hazard ratio [HR], 2.05; P=0.013) and after PSM (HR, 3.41; P=0.007). Lung volumes receiving 5GyE was identified as the strongest predictor for SRL before (odds ratio [OR], 1.04; P=0.005) and after PSM (OR, 1.11; P=0.017). Subsequent analysis excluding dose-volume parameters revealed that PBSPT significantly reduced SRL (OR 0.15, P=0.007).

PBSPT reduced irradiated lung volumes and consequently, reduced SRL. Reducing SRL through optimization of RT techniques might be essential to improve outcomes of locally advanced NSCLC.
Keywords: Lymphopenia, Proton beam therapy, Radiation therapy, Lung cancer
RADIATION TO PRIMARY LESIONS IN PATIENTS WITH NON-OLIGOMETASTATIC NON-SMALL CELL LUNG CANCER WITH EGFR MUTATION WHO DO NOT PROGRESS AFTER TKI, RESULTS OF A PHASE II STUDY

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At present, some studies have confirmed that for patients with stage IV lung cancer with oligometastasis and no progression after systematic treatment, local treatment can bring longer survival time, but relevant reports have not been seen for patients with non-oligometastasis. We performed a phase II study to assess the effect of radiation to primary lesions in patients with non-oligometastatic NSCLC with EGFR mutation-positive who did not progress after EGFR-TKI treatment.

Patients were eligible if they were adenocarcinoma NSCLC with EGFR mutation, had biopsy-confirmed stage IV, 1) > 3 metastases, and 2) no RECIST progression after 3 months underwent first line TKI treatment both primary and metastasis lesion. 3) Appropriate TKI was defined as ≥3 months of erlotinib/crizotinib for patients. 4) The primary tumor can undergo radiotherapy. PFS and OS were assessed the time to developing a new lesion was calculate with a log-rank test. RT dose were two types depending on the location of primary lesion: Central lesion: 60Gy in 20fractions/2weeks, 3Gy in fraction, Peripheral lesion: 50Gy in 10fractions/2weeks, 5Gy in fraction. All efficacy analyses were based on the intention-to-treat analysis. Safety analyses were done on a per-protocol basis, according to treatment that the patients actually received. The study is registered in clinicaltrials.gov (NCT03153358).

Between May 2017 and December 2018, Thirty-one eligible patients were enrolled to receive radiotherapy. The median follow-up for PFS was 20.7 months for all patients. The mean age was 61 years (range: 41–78 years). Eighteen and 13 had mutations at sites 19del and L858R, respectively. Ten and 21 patients were treated with tarceva and ibressa, respectively. The median PFS and OS was 24.6 months(95% CI: 17.6-31.6months) and 43.9 months (95% CI: 31.1-57.8 months). Local lesions in 2/31 patients have progression with 6 month and 19 months after radiotherapy. 20 patients have other organ progression, 10/20 have brain metastases. The gender, PS status, age,
mutation site and efficacy of targeted drugs and the type of radiation had no effect on the prognosis. 10% of patients reported Grade 3 toxicity. no Grade 4-5 toxicity was found.

In non-oligometastatic with EGFR mutation (> 3 mets) without progression after TKI treatment, Radiotherapy to primary lesions resulted in superior local control of the primary disease without an increase in major toxicity. Radiotherapy for these patients could bring longer PFS and overall survival. The findings of this trial suggest that Radiotherapy should be the treatment of choice for this patient group.

Keywords: NSCLC Stage IV, EGFR mutation, TKI treatment, NON-OLIGOMETASTATIC, Radiation, SBRT
PREDICTION OF DELAYED LYMPHOPENIA AT THE TIME OF CONSOLIDATION IMMUNOTHERAPY AFTER CHEMORADIOThERAPY IN LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER

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Consolidation immunotherapy becomes a new standard treatment after definitive chemoradiotherapy (CRT) in locally advanced non-small cell lung cancer (NSCLC). However, the efficacy of immunotherapy can be compromised by treatment-related immune suppression status. We aimed to evaluate clinical and dose-volumetric predictors of delayed lymphopenia at the time of consolidation immunotherapy after CRT in locally advanced NSCLC.

We retrospectively reviewed 279 patients with locally advanced non-small cell lung cancer who received definitive CRT from January 2012 to December 2018. Absolute lymphocyte count (ALC) was recorded at baseline, during CRT, and 1 to 3 months after CRT. Dose-volume histogram parameters for planned target volume, whole body, heart, lung, great vessels, spleen, and thoracic vertebral bodies were evaluated. Dose-volume histogram parameters reported as mean, maximum, and minimum dose with volume receiving 5 Gy (V5), 10 Gy (V10), 20 Gy (V20), 30 Gy (V30), 40 Gy (V40), 50 Gy (V50), and 60 Gy (V60). Overall survival (OS) was analyzed using Kaplan-Meier survival analysis, log-rank test, and Cox regression model. Area under the receiver operating characteristic curve (ROC) analysis and multivariate logistic regression were used to determine the predictors of severe lymphopenia.

Grade 3 lymphopenia (ALC nadir < 500/mm3) were 81.9%, 45.0%, 11.8%, and 16.3% cases and grade 4 lymphopenia (ALC nadir < 200/mm3) were 26.4%, 13.4%, 5.9%, and 8.7% cases during CRT, 1 month, 2 months, and 3 months after CRT, respectively. Kaplan-Meier survival curves revealed that patients with delayed severe lymphopenia (grade 4 lymphopenia during 1 to 3 months after CRT) had the worst prognosis (P<0.0001). Delayed severe lymphopenia was associated with inferior overall survival in multivariate analysis (hazard ratio = 2.96, P < 0.001). On multivariable logistic regression analyses, lung V5 (OR=4.656; p=0.003), mean splenic dose (OR=3.13; p=0.029), lower absolute lymphocyte counts during CRT (OR=0.996; p=0.019), and long smoking history (pack-years; OR =1.037, p = 0.001) were significant predictors for delayed severe lymphopenia. The prediction nomogram was developed according to the above four independent variables. The AUC value of the nomogram model was 0.873.

Delayed lymphopenia is an independent predictor of poor overall survival. Lung V5, mean splenic dose, smoking history, and lymphopenia during CRT revealed as the dominant contributor to delayed lymphopenia at the time of consolidation immunotherapy after definitive chemoradiotherapy.

Keywords: Lymphopenia, Chemoradiotherapy, Locally advanced non-small cell lung cancer
INTRAOPERATIVE ELECTROMAGNETIC NAVIGATION WITH PERCUTANEOUS LOCALIZATION (EMPL) FOR PULMONARY NODULES

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Background: Identification of pulmonary nodules during minimally invasive surgery can be challenging. Reported techniques include hook wire placement, navigation bronchoscopy with dye marking and/or fiducial placement. However, these techniques usually require a separate procedure before surgical resection. We report an alternative approach using electromagnetic navigation with percutaneous localization (EMPL) with indocyanine green (ICG) injected by the surgeon at the time of operation.

Methods: On the day of surgery, CT scan was performed in the lateral decubitus position. Following transfer to the operating room, injection of ICG was undertaken using EMPL. Robotic-assisted minimally invasive resection of the target lesion was then performed using near infrared imaging technology. Nodule characteristics, distance from pleura, and time taken for EMPL were recorded. Primary success was defined as the identification of the target lesion within the initial EMPL-guided wedge or segmental resection specimen.

Results: Over a 3-year period, 35 patients underwent EMPL guided resection lung nodules. There were no complications associated with EMPL. Mean nodule size was 1.1 (range 0.4-2) cm. Mean distance to pleura was 1.1 (range 0.1-2.5) cm. The mean amount of time taken to perform EMPL was 14 (2-27) minutes. The primary success rate of EMPL was 33/35 (94%). Localization failed in 2 patients. The nodule was not present within the initial resection specimen and both patients underwent lobectomy.

Conclusions: Intraoperative localization with image guided percutaneous ICG can be performed safely by thoracic surgeons, and adds minimal time to the operating procedure. In our experience, the primary success rate of nodule localization using EMPL was 94%.
THE PATIENT-CLINICIAN DISCREPANCY OF PERCEPTION ON SYMPTOMS AFTER LUNG CANCER SURGERY FOR PATIENTS

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Patients undergoing surgery for lung cancer suffer a variety of symptom burdens and interference of daily function after surgery. This study aimed to systematically explore lung cancer patients’ account of postoperative experiencing. The purpose of this study is to generate the measurement items of symptoms burden and daily function interference of patients after lung cancer surgery through qualitative interview, so as to lay a foundation for the subsequent development of a Perioperative Symptom Assessment for Lung Cancer (PSA_LC) with specificity, sensitivity and feasibility. Meanwhile, to investigate clinicians’ perception of the burden of symptoms in patients with lung cancer after surgery, and to explore the differences between patients and medical staff in the perception of symptoms related to lung cancer surgery.

Qualitative semi-structured interviews were conducted between June 2018 to October 2019 with 39 patients underwent surgery and were pathologically confirmed as having primary lung cancer, from Sichuan Cancer Hospital in southwest of china. Medical staff were asked to fill out open questions for their perception of symptoms related to the lung cancer surgery. Types and frequencies of symptoms were respectively summarized by hospitalization and within 3 months after discharge, only on clinicians’ view.

Thirty-nine patients (24 females and 16 males, aged between 42 and 82) were interviewed and 22 clinicians (9 surgeons and 13 nurses) with ≥5 years of experience in the department of thoracic surgery filled out survey forms. The five symptoms most frequently mentioned by patients were pain, coughing, distress, shortness of breath, and disturbed sleep. Among those, 4 were perceived by clinicians, while distress was replaced by fatigue, suggesting consistency with 3 months after discharge. However, during hospitalization the five most commonly mentioned were pain, coughing, shortness of breath, chest tightness, fatigue and disturbed sleep (fatigue tied with disturbed sleep for the fifth).
The consensus of primary symptoms between medical staff and patients is pain, cough, shortness of breath, fatigue and poor sleep. The attention of distress is the major discrepancy, which are rarely willed to add into Patient-report-outcomes Scale from clinicians.

**Keywords:** Symptom, Patient-clinician perception, Lung cancer, Surgery
EPIDERMAL GROWTH FACTOR RECEPTOR (EGFR) MUTATION STATUS AFFECTS THE DYNAMIC PATTERN OF SITE-SPECIFIC RECURRENCE IN CURATIVELY RESECTED LUNG ADENOCARCINOMA PATIENTS

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To examine whether epidermal growth factor receptor (EGFR) mutation status affects the pattern and timing of site-specific recurrence after a potentially curative resection for lung adenocarcinoma (ADC).

A total of 366 patients with ADC who underwent complete resection at Peking University People’s Hospital between 2008 and 2018 were included. Site-specific recurrence dynamics according to EGFR mutation status, based on the hazard rate, were evaluated.

We identified 196 patients (53.6%) with EGFR-mutated and 170 (46.4%) EGFR-wildtype lung adenocarcinoma. A total of 85 patients suffered from recurrence, with 43 patients recurred at chest (thoracic cavity), 18 patients recurred in brain and 23 patients recurred in bone. The overall recurrence hazard rate curve (Figure 1A) displayed an initial surge that peaked about 10-12 months after surgery in EGFR-wildtype group. In EGFR-mutated group, the peak occurred 30-32 months after surgery, which was about 20 months later than the peak in EGFR-wildtype one. Besides, EGFR-mutated group showed higher hazard rate than EGFR-wildtype one during the later follow-up. The chest and bone recurrence hazard rate curve showed similar result (Figure 1B and 1D). However, brain recurrence hazard rate curve (Figure 1C) displayed similar peak times after surgery in both EGFR-mutated and EGFR-wildtype groups, with higher hazard rate in EGFR-mutated group.

Different post-operative recurrence patterns were seen in EGFR-mutated and EGFR-wildtype groups. The times with the highest risk of recurrence were suggested to differ according to EGFR mutation status. Site-specific recurrence patterns were also different in EGFR-mutated and EGFR-wildtype groups.

Keywords: Lung adenocarcinoma, Epidermal growth factor receptor, Dynamic pattern, Recurrence, Site-specific recurrence
Figure 1. Recurrence hazard curves according to EGFR mutation status for different recurrence sites: (A) overall recurrence; (B) chest recurrence; (C) brain recurrence; (D) bone recurrence.
NOVEL 3-DIMENSIONAL IMAGE SIMULATION FOR THORACOSCOPIC LUNG SEGMENTECTOMY IN PATIENTS WITH PULMONARY MALIGNANCY

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Pulmonary segmentectomy has been one of a standard surgical procedure in thoracic surgery, which is a technically more complicated procedure than lobectomy because of need to identify variances in pulmonary vessels and the intersegmental line. We have developed a novel simulation system based on high-quality 3D lung modelling from CT images using REVORAS® system (Ziosoft, Inc, Tokyo, Japan). The aim of this study is to evaluate clinical efficacy of the 3D image simulation by the new software in performing thoracoscopic segmentectomy.

We prospectively enrolled 20 patients with pulmonary malignancy for whom thoracoscopic segmentectomy was planned between February and October in 2020. The new 3D-CT software can construct 3D pulmonary and bronchovascular images quickly and generate a proposal for the appropriate segments to be resected from single phase contrast enhanced CT images. Stump view mode, which is an optional view mode of segmentectomy simulation view, helps us view and understand vessels and bronchus after dissection in actual order of the operative procedures. We evaluated anatomical validity and consistency with operative findings of the 3D image on a three points scale, respectively. The time taken to make a 3D image (T1) and a segmentectomy simulation view (T2) were also evaluated.

Of 20 enrolled patients, 13 were diagnosed as primary lung cancer, 5 were diagnosed as metastatic lung tumor, and 2 were diagnosed as benign tumor. The 3D image was evaluated as “good” for anatomical validity in 19 cases (95 %) and for consistency with operative findings in 18 cases (90 %), respectively. Mean time of T1 and T2 were 1min 54 sec and 13 sec, respectively.

Although this study included a limited number of cases, the novel 3D image simulation by REVORAS® system seemed to be easy to prepare, anatomically reliable, and therefore determined to be potentially useful.

Keywords: Segmentectomy, 3-dimensional image simulation
3D Segmentectomy simulation

Stump view mode
Both of microcoil localization and hookwire localization have been proved as good preoperative CT-guided techniques to guide video assisted thoracoscopic resection for small peripheral pulmonary nodules. Retrospective data suggested that microcoil localization was associated with fewer complications compared with hookwire. However, there is no available prospective data comparing these two methods. Hence, we conducted this trial to compare the procedure-specific complication rate of microcoil localization with hookwire for pulmonary nodules.

Patients planning for preoperative localization of small pulmonary nodules were assigned 1:1 for microcoil localization and hookwire localization in this trial. Main inclusion criteria were pure ground-glass nodules, deep solid nodules ≤1 cm and part-solid ground-glass nodules with a solid portion ≤1 cm. Patients combined with pneumothorax, pleural effusion, history of hemoptysis or any medical condition that the radiologist and surgeon disagree for inclusion were excluded. The primary outcome measure was procedure-specific complication rate after CT-guided localization.

In total, 72 participants were assigned to intervention in this study, 36 for microcoil localization, and 36 for hookwire localization. There were no significant differences in demographic and clinical characteristics. Compared with hookwire group, the overall complication rate of microcoil group was significantly lower (30.6% vs. 58.3%, p = 0.033). The incidence of pneumothorax was lower in microcoil group (19.4% vs. 58.3%, p = 0.002), while no significant difference was found between the two groups regarding the incidence of hematoma or hemoptysis. One patient in hookwire group failed to complete the procedure due to newly-diagnosed pneumothorax after local anesthesia. One patient in microcoil group experienced implant dislocation during the following surgery. No patients received further intervention for procedure-specific complications. All the nodules were successfully removed by thoracoscopic surgery. The logistic regression model demonstrated patients underwent hookwire localization had significant higher risk for post-localization complications (OR 3.182, 95% CI 1.228-8.641, p = 0.019) compared with microcoil group.

Both microcoil and hookwire have been proved to be effective in preoperative CT-guided localization for small pulmonary nodules. Localization procedures with microcoil were associated with less complications comparing with hookwire.

Keywords: Pulmonary nodule, Microcoil, Hookwire, Localization
TARGETED NGS APPLICATION TO EVALUATE RECURRENT IMPACT IN RESECTED EGFR-MUTATED LUNG ADENOCARCINOMA

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Targeted next-generation sequencing (NGS) is widely applied in personalized therapy of advanced lung adenocarcinoma patients to identify driver oncogenes, but it also can be applied to resected early stage patients. We investigated mutation profile of resected EGFR-mutated lung adenocarcinoma to evaluate prognostic and recurrent impact using targeted NGS analysis.

Tissues from 131 patients who had complete resection of stage I to IIIA EGFR mutated lung adenocarcinoma (median follow-up: 50.1 months) were analyzed by targeted NGS with 207 cancer-related genes. Recurrence-free survival (RFS) according to genetic alterations was estimated using the Kaplan-Meier method and Cox proportional regression analysis.

The relapses rate was 25.2% (33/131). 5-year RFS of stage IA, IB, II and IIIA was 82%, 75%, 35% and 0% (p<0.001). RFS was proportionally decreased according to the number of accompanying co-mutations. (p=0.025). Among co-mutations, the CTNNB1 mutation was associated with short RFS in a multivariate analysis (hazard ratio [HR]: 5.4, 95% confidence interval: 2.1-14.4, p=0.001). TP53 was also associated with short RFS in stage IB-IIIA. (p=0.01) RFS of exon 19 deletion was shorter than RFS of L858R in stage IB-IIIA tumors (p=0.008). Of exon 19 deletion sub-types, pL747_P753delins (6/56, 8.9%) had shorter RFS than the most frequent pE746_A750del (39/56, 69.6%) (p=0.004)

Targeted NGS analysis reveals that the number of concomitant mutations, CTNNB1 co-mutation, and the subtype of exon 19 deletion especially, pL747_P753delins, were negative prognostic factors for recurrence and can be used as a novel platform to predict prognosis and recurrence in resected EGFR-mutation lung adenocarcinoma patients.

Keywords: EGFR mutation, Recurrence, Next-generation sequencing, CTNNB1, Lung adenocarcinoma
Education Session IX.
Targeted Therapies for Lung Cancer

Chair: Sang-We Kim (Korea)
Evolution of Acquired Resistance to Targeted Therapies for Lung Cancer

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Acquired drug resistance to even the most effective lung cancer targeted therapies remains an unsolved clinical problem. Although many drivers of acquired drug resistance have been identified, our understanding of the fundamental mechanisms influencing tumor evolution during treatment is still incomplete. While pre-existing resistant clones may emerge under the selective pressure of therapy, cancer cells can also adapt and evolve in response to treatment. Here, we will discuss how drug tolerance and adaptive mutability can contribute to the evolution of acquired resistance to lung cancer targeted therapies.
Crizotinib was the first approved tyrosine kinase inhibitor that showed activity in the treatment of ALK and ROS1-positive lung cancer. However, acquired resistance occurs due to inadequate CNS concentration of crizotinib and emergence of resistant mutations. New ALK inhibitors such as ceritinib, alectinib, brigatinib, ensartinib, and lorlatinib have been developed to overcome the crizotinib resistance in second or later line setting and these agents eventually became the first line treatment. For ROS1-positive lung cancer, ceritinib, entrectinib, lorlatinib, and repotrectinib have been reported as an active agent in clinic. I will discuss on the efficacy and toxicity profiles of current treatment options.
Treatment for Advanced MET, RET-Altered Lung Cancer

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Recent advance of treatment of advanced non-small cell lung cancer is mainly achieved by either drastic advance by emergence of PD-1/PD-L1 inhibitors and steady expand in repertoire targeted genes treated with their inhibitors. MET and RET was long waited target to be clinically treated by its inhibitors. MET alteration in lung cancer has been considered especially as the bypass signaling in EGFR-TKI resistance. Several MET inhibitors have shown partial efficacy in this situation with no confirmed evidence to support the use of MET inhibitors in this setting. Discovery of MET exon 14 skipping has accelerated the development of MET inhibitors. High response rate was shown in phase 2 studies of capmatinib and tepotinib, and concluded to the approval. RET translocation and mutation is found to be the oncogenic mainly in thyroid and lung cancer, but most of the tested inhibitors could not show the adequate efficacy to be approved with phase 2 study. Selpercatinib and pralsetinib now showed response rate of more than 60% and become the pioneer of RET treatment.
Huge advances for the treatment of advanced lung cancer have been through a great in-depth and genomic researches. Many things have been changed in clinical practice and now we are approaching the customized treatment for each advanced lung cancer. Aside from the major gene alterations such as EGFR or ALK, which has drugs that have already made a big achievement in terms of survival, there are many minor mutations searching for the best therapeutic agents and also the best results. In this educational session, I will review some of the key developments and novelties in the treatment of advanced lung cancer with minor gene alterations including BRAF, MEK, HER2, NTRK etc.
Satellite Symposium V.
Takeda Pharmaceuticals Korea CO., Ltd.

Chair: Dae Ho Lee (Korea)
A Paradigm Shift in ALK+NSCLC First-line Treatment : Emerging Role of Brigatinib

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The treatment landscape of ALK+ NSCLC is rapidly evolving. About 2–7% of NSCLC is driven by the fusion protein between echinoderm microtubule-associated protein-like 4 (EML4) and anaplastic lymphoma kinase (ALK). The first ALK-inhibitor approved for the treatment of NSCLC was crizotinib with an ORR up to 74%. Following phase III trial comparing crizotinib with chemotherapy showed significant improve PFS leading to approval as first line. Since then, multiple next generation ALK inhibitors, ceritinib, alectinib, brigatinib and lorlatinib which have broad activity against ALK resistance mutation and high CNS activity have been developed. Currently, alectinib, brigatinib, ceritinib, and crizotinib have been approved as first line therapy. Lorlatinib granted approval as post-crizotinib or salvage therapy.

Alectinib is approved by the US FDA for the first-line treatment of patients with ALK-positive metastatic NSCLC as detected by an FDA-approved test. The latest NCCN guideline recommended the alectinib as preferred first-line therapy and brigatinib as category1 recommended regimen as first-line. In ALEX study, alectinib showed significantly improved PFS compared with crizotinib. By independent review, PFS was 25.7 vs 10.4m for crizotinib. In contrast, by investigator assessment, PFS was 34.8m for alectinib vs. 10.9m for crizotinib, which is longer than independent review. In terms of CNS activity, according to primary analysis. According to the final analysis, the median PFS was 25.4m for alectinib vs 7.4m for crizotinib HR 0.37 in patients with baseline CNS metastases. The median PFS was 38.6m for alectinib vs 14.8m for crizotinib HR=0.46 in patients without CNS metastasis.

Brigatinib is a next-generation ALK inhibitor that targets a broad range of ALK mutations, and has demonstrated improved efficacy over crizotinib the first-line treatment of ALK-positive, advanced NSCLC. Brigatinib received FDA approval as a first-line treatment option for patients with advanced (stage IV) NSCLC based on the phase 3 ALTA 1L study. It has shown comparable activity to alectinib the first-line setting, but direct comparisons are lacking. Although brigatinib is associated with pulmonary toxicity in a small percentage of patients, this risk can be ameliorated by step-up dosing.
In a phase III trial including 275 patients with advanced, treatment-naïve, ALK-positive NSCLC, those randomly assigned to brigatinib experienced an improvement in PFS over those assigned to crizotinib (12-month PFS rate of 67 versus 43 percent for brigatinib versus crizotinib, respectively (HR 0.49), at a median follow-up of between 9 and 11 months; median PFS of 24 versus 11 months, respectively (HR 0.49). Even greater PFS benefits were observed among those with baseline brain metastases. ORR were 79 percent with brigatinib versus 75 percent with crizotinib. Among those with brain metastases at baseline, the intracranial response rate was significantly higher with brigatinib (78 versus 26 percent).

Recently, CROWN study, a phase III randomized study of lorlatinib vs crizotinib as first-line therapy was reported in ESMO2020. Advanced ALK+ NSCLC patients are randomized either lorlatinib or crizotinib and primary endpoint is PFS by independent review. Lorlatinib resulted in a significantly longer PFS, significantly higher overall and IC response rates, and improved global QoL compared to crizotinib in first-line, treatment-naïve ALK+ NSCLC. Overall survival was immature, with medians not reached in either treatment arm. The hazard ratio was 0.72, with a 95% confidence interval of 0.41 to 1.25. We need to more longer follow up.

Currently, the first line ALK+ NSCLC data are all compared to crizotinib, 1st generation ALK inhibitor. There was no data comparing head to head comparison between 2nd generation ALK inhibitors or 3rd generation ALK inhibitors.
Satellite Symposium VI.
Roche Korea

Chair: Byoung Chul Cho (Korea)
Long Term Results of First Line Atezolizumab for Patients with Extensive Stage Small Cell Lung Cancer

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Since etoposide plus platinum, treatment in extensive stage-small cell lung cancer (ES-SCLC) has been remained without any significant progress, including that anti-CTLA4 ipilimumab to chemotherapy was failed to show any survival benefit in IN CA184-156 study[1]. Recently, results from several phase 3 trials in ES-SCLC have been released and shown benefit of adding anti-PD(L)1 to chemotherapy. The first successful trial was IMpower133[2], which compared atezolizumab plus etoposide/carboplatin (EC) with EC. Adding atezolizumab prolonged both progression free survival (PFS) and overall survival (OS) significantly. Median PFS was 5.2 months in atezolizumab+EC arm compared with 4.3 months in EC arm, and updated median OS[3] was 12.3 months vs. 10.3 months (HR 0.76, p=0.0154). Now immune checkpoint inhibitor combination is a new standard of 1st line treatment in ES-SCLC. Later released two more phase 3 trials, CASPIAN trial[4] demonstrated OS benefit, which was primary endpoint of the trial, of adding durvalumab to etoposide and platinum in ES-SCLC. Pembrolizumab and chemotherapy combination improved median PFS to 4.5 months versus 4.3 months in ES-ECLC, however significance threshold for OS benefit was not met in KEYNOTE-604 trial[5]. This review will summarize the main and updated results of 1L trials in ES-SCLC, mainly from IMpower133, and discuss clinical issues related to the use of immune checkpoint inhibitors in real world.
Policy Symposium.
Tobacco Controls in US, Europe, and Asia

Chair: Seung Hun Jang (Korea)
In the summer of 2019, the first case of severe pulmonary disease associated with the use of electronic (e-cigarette) products was reported to the US Center for Disease Control and Prevention (CDC). The use of these products had been increasing in the preceding years since their introduction to the US market in 2007. This lung injury has been named e-cigarette, or vaping, product use-associated lung injury (EVALI). This illness presents with shortness of breath, cough, and fever, similar to community-acquired pneumonia or COVID-19. The majority of patients are young adults and male. Chest imaging demonstrates diffuse or hazy opacities in both lungs. When hospitalized for the illness, about 25% of patients will undergo invasive mechanical ventilation in the management of respiratory failure. Antimicrobial and glucocorticoid therapy are commonly used. About 2% of hospitalized patients have died.

The underlying lung pathology have manifested various patterns including diffuse alveolar damage, acute fibrinous pneumonitis, organizing pneumonia, lipoid pneumonia, acute eosinophilia pneumonia, and diffuse alveolar hemorrhage. The etiopathogenesis of EVALI remains unclear. Among the suspected causes are vitamin E acetate (commonly added to e-liquid as a diluent), and byproducts of pyrolysis.

The diagnostic criteria for EVALI includes: 1) use of an e-cigarette, or vaping, product during the 3 months before symptoms onset, 2) pulmonary infiltrates on chest imaging, 3) absence of pulmonary infection, and 4) absence of a more likely alternative diagnosis.
Heated tobacco products (HTPs) such as IQOS and Ploom Tech have rapidly become popular in Japan, but their impact on smoking cessation practices is not fully understood. To consider the influence of HTPs on smoking cessation practices, we compared the proportion of different methods used by smokers in their attempts to quit during 2016 and 2018, i.e. before and after the widespread use of HTPs in Japan. We conducted an internet survey of the Japanese general population from January to March of 2016 and 2018 (the JASTIS study 2016, 2018) and analyzed 133 (2016) and 376 (2018) smokers who attempted to quit smoking at least once within the previous year (quit attempters).

The percentages of each quit method implemented by the 133 quit attempters in 2016 were 21.8% for over-the-counter smoking cessation aids, 14.3% for smoking cessation treatment at smoking cessation clinics, 25.6% for electronic cigarettes and/or HTPs, and 72.2% for unassisted quitting (i.e. quitting without pharmacological aids or other interventions). Next, the percentages of each quit method among the 376 quit attempters in 2018 were found to be 22.9% for over-the-counter smoking cessation aids, 15.2% for smoking cessation treatment at smoking cessation clinics, 51.6% for HTPs, 27.7% for electronic cigarettes, and 42.3% for unassisted quitting. Collectively with “electronic cigarettes and/or HTPs,” the figure was 64.1%.

From 2016 to 2018, the percentage of electronic cigarettes and/or HTPs used as quit methods increased from 25.6% to 64.1%, with HTPs being the most common quit method in 2018 at 51.6%. There has been a decreasing tendency in the number of smoking cessation visits in Japan as HTPs have become more popular. This may be due in part to the tobacco industry’s promotion of HTPs, which has resulted in quit attempters trying HTPs instead of quitting cigarettes.
The increased tobacco tax policy to aid in quitting smoking increased the price of cigarettes. Generally, an association has been seen between the rise in cigarette price and a decrease in smoking.

The Korean government increased the price of cigarettes by 2,000 won (approximately $2 USD) in 2015 in order to reduce the rate of male smokers in the country. Since then, the rate of male smokers has dropped from 43.7% in 2014 to 36.7% in 2018.

The budget received from the increased tobacco tax has been used by the National Health Insurance Service for smoking cessation treatments and various programs for different levels of smokers, such as outpatient treatment and short-term smoking cessation camps, that are run by smoking cessation support centers supported by the Korean Health Promotion Development Center.

Patients can attend smoking cessation clinics where they are able to meet with a physician for three months per cycle, with up to three cycles per year. They can receive full coverage for their medication and consultation fees from their national health insurance.

COVID-19 is an infectious disease caused by SARS-CoV-2, which is generally spread by droplets from coughing and sneezing. The incubation period of the virus is usually 4-5 days but can range from 1-14 days. The symptoms vary from asymptomatic cases to fever, cough, fatigue, and dyspnea. Globally, there have been approximately 40 million people infected and over a million deaths from the virus, and presently the second wave of the pandemic is ongoing.

It is a common behavior for smokers to take off their masks in crowded smoking areas and frequently touch their mouths. This is a very easy way to directly infect oneself with the COVID-19 virus and also indirectly infect others around them with the virus through secondhand smoke.
The nicotine that is contained in cigarettes increases the number of ACE2 receptors (Angiotensin-Converting Enzyme 2), which are abundant in the lungs, heart, and vascular endothelium, and attach to the spike protein of COVID-19.

In the case of smokers who smoke cigarettes combined with e-cigarettes, the chance of being infected with COVID-19 is 7 times higher than that of non-smokers.

There was a significant association between smoking and progression of COVID-19 related symptoms (OR 1.91, 95% confidence interval [CI] 1.42-2.59, p = 0.001). Mortality related to COVID-19 among smokers was 29.4% compared to 17.0% among non-smokers and RR was 2.07 (95% CI: 1.59, 2.69). Despite the increased risk of COVID-19 associated with smoking, there has been no significant change in the use of nicotine products worldwide. Additionally, in Korea, during the first half of the year, there was an increase in sales of nicotine products. However, the sales of e-cigarettes decreased due to the government’s campaigns advertising the adverse effect of e-cigarettes such as acute lung injuries.

Currently, it has become more difficult to attend programs for smoking cessation due to the COVID-19 situation, and there has been an increase in non-face-to-face marketing by cigarette companies. Therefore, it is imperative to support campaigns for smoking cessation and stress the dangers of smoking associated COVID-19 to the public.
Pharmacotherapy for Smoking Cessation and Nicotine Dependence

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Cigarette smoking is a preventable cause of death. However, success rates of smoking cessation are low compared to willingness to quit smoking. Thus, additional support will be needed to quit smoking such as behavioral therapy and pharmacotherapy. Pharmacotherapy include nicotine replacement therapy (NRT), bupropion, varenicline and etc. NRT relieves nicotine withdrawal symptoms by providing nicotine without the use of cigarette. NRT products are either long acting nicotine transdermal patch or short acting gum, lozenge, inhalers, nasal spray, mouth spray and sublingual tablet. Their different bioavailability allows combination therapy of NRT products to increase efficacy for quit smoking. Bupropion enhance central nervous system noradrenergic and dopaminergic release. Varenicline bind with the alpha-4 beta-2 nicotinic receptor and act as a partial agonist to blocks nicotine binding. It reduces the nicotine withdrawal symptoms. In here, mechanism, administration, efficacy, and side effects of pharmacotherapy and combination therapy for smoking cessation will be presented.
Poster Presentation
DIAGNOSTIC AND PREDICTIVE VALUES OF 18F-FDG PET/CT
METABOLIC PARAMETERS IN EGFR-MUTATED ADVANCED LUNG
ADENOCARCINOMA

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The clinical implications of the metabolic parameters of 18F-fluorodeoxyglucose positron emission tomography-computed tomography (18F-FDG PET/CT) in epidermal growth factor receptor (EGFR)-mutated lung cancer are not fully understood. The aim of this study was to evaluate the diagnostic and prognostic utility of the parameters in EGFR-mutated lung cancer patients.

We retrospectively enrolled 134 patients with advanced lung adenocarcinoma (72 EGFR-negative and 62 EGFR-positive). We evaluated the correlation between EGFR mutational status and the maximum standardized uptake value (SUVmax), as well as the associations between treatment outcomes in EGFR-mutated patients and various metabolic parameters of primary tumors. For the best predictive parameters, we calculated the metabolic tumor volume (MTV) and total lesion glycolysis (TLG) using two SUV cutoffs: 1.5 (MTV1.5, TLG1.5) and 2.5 (MTV2.5, TLG2.5).

Mean SUVmax was lower for EGFR-mutated tumors compared with EGFR wildtype (6.11 vs 10.41, p < 0.001) tumors. Low SUVmax was significantly associated with positive EGFR mutation (odds ratio = 1.74). Multivariate analysis for survival demonstrated that high MTV1.5, TLG1.5, MTV2.5, and TLG2.5 were independently associated with shorter progression-free survival (PFS) and overall survival (OS), and the highest hazard ratios were found in TLG1.5 (3.26 for PFS and 4.62 for OS).

SUVmax may be predictive for EGFR mutational status, and MTV and TLG of primary tumors may be promising prognostic parameters; 18F-FDG PET/CT has potential utility for the risk stratification of EGFR-mutated patients treated with targeted therapy.

Keywords: Lung cancer, 18F-FDG PET/CT, Metabolic parameters, EGFR
WHO WILL MAINTAIN AS LONG-TERM RESPONDERS MORE THAN 3 YEARS WITH FIRST- OR SECOND-GENERATION EGFR TKI AMONG EGFR MUTANT NSCLC?

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Although osimertinib is preferred first-line EGFR tyrosine kinase inhibitor (TKI) in patients with EGFR mutant non-small cell lung cancer (NSCLC) based on longer progression free survival (PFS) and high CNS efficacy, other first or second generation EGFR TKIs (gefitinib, erlotinib or afatinib) still remain as treatment options. Since long-term responders (LTR) with first or second generation EGFR TKIs are often noted in proportion of patients in real world, it would be valuable to determine patient characteristics associated with long-term responders considering sequential approach of EGFR TKI in the management of EGFR mutant NSCLC.

We analyzed EGFR-mutant advanced NSCLC patients treated with first-line gefitinib, erlotinib or afatinib from Jan 2013 to Dec 2016. LTRs were defined as patients whose PFS is longer than 36 months. We compared patient characteristics and other clinical outcomes between LTR group and control group.

Of the 931 patients treated with first-line EGFR-TKI other than osimertinib, 140 (15.0%) patients were LTRs; gefitinib (n=85, 60.7%), erlotinib (n=22, 15.7 %), and afatinib (n=33, 23.6%), respectively. With median follow-up of 59.5 months, median PFS was 54.1 months and overall survival was not reached in the LTR group. Patients with recurrent disease (OR 0.40, p<0.001), Exon 19 deletion (OR 0.58, p=0.007) and without distant metastases of wet pleura (OR 3.10, p<0.001), bone (OR 1.83, p=0.003), CNS (OR 1.69, p=0.018) and other extra-thoracic organ (OR 7.08, p=0.001) were associated with LTRs.

In real world data, 15% of patients can achieve more than 3 years of treatment duration with first- or second-generation EGFR TKI alone. Given insufficient availability of osimertinib as first-line therapy in many countries and lack of established salvage therapy against osimertinib-resistant NSCLC, our results suggest that first or second generation EGFR TKIs can be considered for patients with recurrent disease, exon 19 deletion, and without wet pleura, bone, CNS and other extra-thoracic organ metastases.

Keywords: EGFR-mutant advanced NSCLC, Gefitinib, Erlotinib, Afatinib, Long-term responders
The Lung Immune Prognostic Index (LIPI) utilizes derived neutrophil-lymphocyte ratio (dNLR) and LDH to define prognostic subgroups associated with overall survival (OS) and overall response rate (ORR) to immune-checkpoint inhibitors (Mezquita L et al, JAMA Oncol 2018).

Pre-treated advanced NSCLC pts who received Pembrolizumab (P) at The Christie (Jan ‘17-July ’19) were identified. Baseline demographics, PD-L1 tumour proportion score (TPS), and LIPI score were collected. We assessed progression free survival (PFS) and OS using Kaplan-Meier method and performed a comparative analysis of LIPI score and PD-L1 TPS on survival.

111 consecutive pts were analysed (Table 1 shows baseline demographics). After a median follow up of 11.2 months, 77.5% of pts progressed. ORR was 26.1%. Median PFS and OS were 4 (1.6-6.4) and 13 (10.2-15.8) months (mos), respectively. OS was 10 vs 19 mos (HR 0.50, 95% CI 0.3-0.8; p=0.006) for TPS 1-49% and =50%, respectively. OS for good vs intermediate vs poor LIPI score was 14, 11 and 3 mos (HR 1.5, 95% CI 1.1-2.3; p=0.018), respectively. 36.9% of pts experienced immune related adverse events (irAEs), 10.8% being grade 3-5. Toxicity-related discontinuation rate was 14.4%. LIPI score and high TPS remained prognostic factors in a multivariate model including ECOG, smoking status and irAEs. 40% of pts received = 4 cycles, mostly due to early disease progression (EDP). Pts with EDP had shorter OS (4 vs 19 mos, P<0.005). Next generation sequencing analysis for this subgroup is ongoing.

Our cohort demonstrated similar survival outcomes to KEYNOTE-010, which reflects appropriate patients’ selection. High PD-L1 TPS and LIPI score predicted longer OS.

Keywords: Pembrolizumab, Immunotherapy, LIPI, Biomarkers
Figure 1. Overall survival according to LIPI score (good, intermediate and poor).

Table 1. Demographics

<table>
<thead>
<tr>
<th>Demographics</th>
<th>N 111 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean</td>
<td>65</td>
</tr>
<tr>
<td>≥ 75</td>
<td>20 (18.0%)</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>66 (59.5%)</td>
</tr>
<tr>
<td>ECOG 0-1/2</td>
<td>108 (77.3)/3 (2.7)</td>
</tr>
<tr>
<td>(Ex)-smoker / Never</td>
<td>103 (92.8)/8 (7.2)</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>70 (63.1)</td>
</tr>
<tr>
<td>Squamous</td>
<td>34 (31.5)</td>
</tr>
<tr>
<td>Other/NOS</td>
<td>6 (5.4)</td>
</tr>
<tr>
<td>EGFR</td>
<td>2 (1.8)</td>
</tr>
<tr>
<td>ALK/ ROS1</td>
<td>0 (0)</td>
</tr>
<tr>
<td>KRAS</td>
<td>6 (5.4)</td>
</tr>
<tr>
<td>Biopsy sample for PD-L1</td>
<td></td>
</tr>
<tr>
<td>Archival / Fresh</td>
<td>76 (68.5)/35 (31.5)</td>
</tr>
<tr>
<td>PD-L1 TPS</td>
<td></td>
</tr>
<tr>
<td>1-49% / ≥ 50%</td>
<td>62 (55.9)/49 (44.1)</td>
</tr>
<tr>
<td>Previous lines of treatment</td>
<td></td>
</tr>
<tr>
<td>1 / ≥2</td>
<td>99 (89.2)/12 (10.8)</td>
</tr>
<tr>
<td>Stage at P initiation</td>
<td></td>
</tr>
<tr>
<td>IIIA-B/ IV</td>
<td>12 (10.8)/99 (89.2)</td>
</tr>
<tr>
<td>Metastatic site</td>
<td></td>
</tr>
<tr>
<td>Lung/Pleura</td>
<td>95 (85.6)</td>
</tr>
<tr>
<td>Bone</td>
<td>19 (17.1)</td>
</tr>
<tr>
<td>Liver</td>
<td>16 (14.4)</td>
</tr>
<tr>
<td>Adrenal</td>
<td>11 (9.9)</td>
</tr>
<tr>
<td>Brain metastases</td>
<td>12 (10.8)</td>
</tr>
</tbody>
</table>

1. No patients with active brain metastases
Several studies have shown that STK11 and TP53 mutations have different effects on the susceptibility to immune checkpoint blockade in KRAS-mutant non-small cell lung cancer (NSCLC). However, the impact of STK11/TP53 co-mutations on treatment outcomes in the same clinical setting has never been reported.

We recently encountered a case of a 70-year-old man who was diagnosed with advanced lung adenocarcinoma with high programmed death-ligand 1 (PD-L1) expression. He received pembrolizumab monotherapy as a frontline treatment; however, the tumor did not respond to this therapy and showed deleterious outcome.

Next-generation sequencing revealed that the tumor harbored a rare STK11/TP53/KRAS triple mutation. STK11/TP53/KRAS triple mutations are exceptionally rare; only seven in 1385 NSCLC patients harbored this mutation. To the best of our knowledge, this is the first case describing an adverse clinical outcome after immune checkpoint blockade for NSCLC harboring KRAS/STK11/TP53 co-mutations.

Our case suggests that these compound mutations may constitute a distinct, aggressive subset that is resistant to immunotherapy even when the tumor strongly expresses PD-L1. In addition, this report highlights the importance of using molecular profiling to detect co-mutations that can be associated with primary resistance or disease progression to improve survival even in the immunotherapy setting.

Keywords: Lung cancer, KRAS, STK11, TP53, Immune checkpoint inhibitors, Resistance
ACQUIRED RESISTANCE MECHANISM OF EGFR-KDD AGAINST EGFR TKIS IN NSCLC

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EGFR kinase domain duplication (KDD) was revealed as a novel oncogenic mutation of non-small-cell lung cancer (NSCLC). Unlike common EGFR mutations, EGFR-KDD is not fully understood due to its rareness. Furthermore, there has not been a study on EGFR-KDD with acquired T790M mutation. Hence, we aimed to do a functional study of EGFR T790M-positive KDD (EGFR-KDD¹⁷⁹⁰M).

A 56-year-old never-smoker male was diagnosed with stage IV lung adenocarcinoma harboring EGFR-KDD that was detected by targeted next-generation sequencing. The patient’s tumors initially responded to erlotinib for 8 months and subsequently acquired resistance to erlotinib. EGFR T790M mutation was detected in erlotinib-resistant cells from malignant pleural effusion. We developed a patient-derived cell line (SNU-4784) and screened EGFR TKIs in SNU-4784 cells. In addition, we established various types of EGFR-KDD Ba/F3 cell lines; EGFR-KDD wild type (EGFR-KDDWT), EGFR-KDD domain 1 T790M (EGFR-KDD¹⁷⁹⁰M), EGFR-KDD domain 2 T790M (EGFR-KDD¹⁷⁹⁰M), and EGFR-KDD both domain T790M (EGFR-KDD¹⁷⁹⁰M). We performed cell viability assays, immunoblot assays, and ENU (N-ethyl-N-nitrosourea) mutagenesis screening using EGFR TKIs.

EGFR-KDDWT Ba/F3 cells were sensitive to 2nd generation EGFR TKIs (IC50, < 0.01nM) as well as 3rd generation EGFR TKIs (IC50, 0.07 ± 0.04 nM, 0.21 ± 0.2 nM). In contrast, only 3rd generation EGFR TKIs were effective against EGFR-KDD Ba/F3 cells with EGFR T790M (IC50, 0.2 ± 0.2 nM ~ 12.1 ± 5.3 nM). These findings were confirmed using immunoblot assays. Next, ENU mutagenesis was performed in EGFR-KDD¹⁷⁹⁰M Ba/F3 cells and an additional EGFR C797S mutation was found only in domain 2 of EGFR-KDD¹⁷⁹⁰M Ba/F3 cells as an osimertinib-resistant mechanism. With this finding, we developed EGFR-KDD domain 1 T790M / domain 2 cis-T790M/C797S (EGFR-KDD¹⁷⁹⁰M / cisT790M/C797S) Ba/F3 model. EAI045 (an allosteric EGFR inhibitor) or brigatinib (ALK/EGFR dual inhibitor) in combination with cetuximab (EGFR antibody) has no efficacy against EGFR-KDD¹⁷⁹⁰M Ba/F3 cells, suggesting a ligand-independency of kinase domain dimerization of EGFR-KDD.

Our study reveals that T790M mutation in EGFR-KDD confers resistance to 1st and 2nd generation EGFR TKIs. In addition, C797S mutation in EGFR-KDD¹⁷⁹⁰M mediates a resistance mechanism against osimertinib.

Keywords: EGFR-KDD, NSCLC, T790M mutation, Acquired resistance
NRAS mutation is observed in 0.7-1.2% of NSCLC patients with few clinical and preclinical data. Although MEK inhibitor monotherapy was moderately active against NRAS-mutant melanoma, there has been no approved treatment for NRAS-mutant NSCLC. In our previous study, we revealed that G2/M phase arrest disrupts the growth of NRAS-mutant NSCLC cells using Human Kinome siRNA and Human Kinome CRISPR libraries screening. In addition, dual blockade of pan-RAF and PLK1 showed a potent efficacy in long-term viability assay. Here, we evaluated the efficacy of pan-RAF inhibitors with AURKA inhibitors in human NRAS-mutant NSCLC cell lines.

Cell proliferations were compared between LXH254 monotherapy and in combination with AURKA inhibitors (alisertib or tozasertib) in human NRAS-mutant NSCLC cells (NRAS Q61K, n=3; NRAS Q61L, n=1). In addition, apoptosis assay was performed by Annexin V staining in HCC15 cells were treated with 1μM LXH254 and 1μM alisertib for 24 h.

Alisertib or LXH254 monotherapy was more toxic to NRAS-mutant NSCLC cells than tozasertib monotherapy (IC50 of LXH254, 1.20 ± 1.11μM; tozasertib, 0.08 to 4μM; and alisertib, 0.038 to >; 5μM). In addition, LXH254 plus AUKRA inhibitors displayed a synergistic effect in NRAS-mutant NSCLC cell lines, except for HCC1195. Furthermore, the apoptotic cells were approximately 3 times higher in the combination group than LXH254 or alisertib monotherapy in HCC15 cells.

We revealed that dual blockade of AURKA and pan-RAF showed a synergistic effect in patient-driven NRAS-mutant NSCLC cells by short-term viability assay and apoptosis assay, suggesting that G2/M phase arrest with inhibition of pan-RAF is promising therapeutic strategy in NRAS-mutant NSCLC patients.

**Keywords**: NSCLC, NRAS, pan-RAF, AURKA
FIRST-LINE (1L) NIVOLUMAB + IPILIMUMAB IN ASIAN PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER (ANSCLC) IN CHECKMATE 227

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In CheckMate 227 Part 1 (NCT02477826), 1L nivolumab (NIVO) + ipilimumab (IPI) improved overall survival (OS) vs platinum-doublet chemotherapy in patients with aNSCLC with a manageable safety profile. We report results from the Asian subpopulation, including patients from Japan, South Korea, and Taiwan.

Patients with stage IV/recurrent NSCLC and PD-L1 =1% were randomized 1:1:1 to NIVO (3 mg/kg Q2W) + IPI (1 mg/kg Q6W), NIVO monotherapy (240 mg Q2W), or chemotherapy. Patients with PD-L1 <1% were randomized 1:1:1 to NIVO+IPI, NIVO (360 mg Q3W) + chemotherapy, or chemotherapy.

Baseline characteristics of Asian patients were generally balanced between NIVO+IPI (n = 121) and chemo (n = 124) arms. Minimum follow-up for OS was 29.7 months (database lock, July 2, 2019). Asian patients with PD-L1 = 1% had a 24% reduction in risk of death (HR, 0.76;95% CI: 0.49–1.17) with NIVO+IPI vs chemotherapy (Table). Median progression-free survival (PFS) was 11.0 months with NIVO+IPI vs 6.7 months with chemotherapy (HR, 0.64; 95% CI: 0.43–0.95). Objective response rates were 54% with NIVO+IPI and 37% with chemotherapy, median duration of response was 26.1 months and 6.9 months, respectively. Among all randomized Asian patients (PD-L1 =1% + <1%), improved efficacy with NIVO+IPI vs chemotherapy was observed (Table). Grade 3–4 treatment-related adverse events (TRAEs) were reported in 40% vs 36%, and any grade TRAEs leading to discontinuation occurred in 22% vs 13% of patients with NIVO+IPI vs chemotherapy, respectively. Updates from a 3-year minimum
follow-up will be presented.

As with the global population of CheckMate 227, the Asian subpopulation had improved efficacy with NIVO+IPI vs chemotherapy as 1L treatment for aNSCLC. Safety in the Asian subpopulation was consistent with the global population.

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**Keywords:** Non-small cell lung cancer, Asian subpopulation, First-line, Nivolumab, Ipilimumab, CheckMate 227

Part 1, Overall Survival, PD-L1

<table>
<thead>
<tr>
<th>Table: Efficacy in the Asian subpopulation of CheckMate 227</th>
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<tbody>
<tr>
<td>Patients with PD-L1 ≥ 1%</td>
</tr>
<tr>
<td>OS, median (95% CI), mo</td>
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<tr>
<td>HR (95% CI)</td>
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<tr>
<td>1-y OS, %</td>
</tr>
<tr>
<td>2-y OS, %</td>
</tr>
<tr>
<td>PFS, median (95% CI), mo</td>
</tr>
<tr>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>ORR, n (%)</td>
</tr>
<tr>
<td>DOR, median (95% CI), mo</td>
</tr>
</tbody>
</table>

| All randomized patients                                         | NIVO+IPI (n = 121) | Chemotherapy (n = 124) |
| OS, median (95% CI), mo                                        | NR (17.8–NR)       | 22.9 (18.2–26.4)       |
| HR (95% CI)                                                     | 0.68 (0.49–0.96)   | –                     |
| 1-y OS, %                                                       | 76                 | 68                    |
| 2-y OS, %                                                       | 53                 | 45                    |
| PFS, median (95% CI), mo                                       | 8.5 (5.5–11.1)     | 5.6 (4.5–7.0)         |
| HR (95% CI)                                                     | 0.66 (0.48–0.90)   | –                     |
| ORR, n (%)                                                     | 57 (47)            | 41 (33)               |
| DOR, median (95% CI), mo                                       | 24.5 (15.0–NR)     | 5.6 (3.7–6.9)         |
| NR, not reached;                                                 |
THE CONTRADICTION OF EGFR MUTATIONS BETWEEN MEN AND WOMEN IN INDONESIA: LITERATURE REVIEWS

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Today, adult men in Indonesia and young people smoke as part of their social life. As a result, the number of lung cancer cases continues to increase dramatically. It is estimated that in 2018, male lung cancer sufferers will be around 14% (WHO data). We discuss the latest research in Indonesia regarding EGFR mutations, which are mutations on the one hand experienced by men and on the other by women.

This study uses an electronic database as a method by reviewing several recent articles that discuss an issue in the 2018 and 2019.

There are two different perspectives on EGFR mutations. First, if a study is performed on cytology specimens to detect EGFR mutations. The result was that women had a higher rate of EGFR mutations (approximately 52.9%) than men (39.1%) and 9% had EGFR complex mutations. Contrast on the second study, where the EGFR mutation was influenced by smoking, which was routine and experienced by many men.

The difference between the two perspectives on the EGFR mutation provides a new view that EGFR mutations can occur in both women and men.

Keywords: EGFR mutasi, Men and women, Literature research, Indonesia
Comprehensive Evaluation of the Clinical Utility of Plasma EGFR Test in Non-Small Cell Lung Cancer Patients with Acquired Resistance to First-Line EGFR Inhibitors

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Plasma epidermal growth factor receptor (EGFR) mutation tests are widely used when non-small cell lung cancer (NSCLC) patients acquire resistance to EGFR inhibitors. We comprehensively evaluated the clinical utility of plasma EGFR test.

We screened NSCLC patients who had a plasma EGFR test upon acquiring resistance to first- or second-generation EGFR inhibitors. Plasma EGFR tests were performed with the EGFR mutation test.

A total of 355 patients were tested for plasma EGFR mutations, and T790M was detected in 83 patients (23%). Of 79 patients who were tested multiple times, T790M was newly detected in 13 subsequent plasma tests. When initial plasma tests did not detect any EGFR mutation types, the detection rate of T790M in subsequent tests was very low (9%, 5/56), while detection rates of T790M in subsequent tests increased (35%, 8/23) in those individuals in whom sensitizing mutations had been detected in the initial plasma test (p = 0.005). Paired plasma and tissue EGFR test results were available for 235 patients. Sensitivity and specificity of the plasma tests for T790M were 14% and 87%, respectively. Among 235 patients, 140 patients had tissue EGFR tests performed after T790M-negative plasma results were reported. The subsequent tissue test detected T790M in 61% (44/72) of these patients when any EGFR mutations were not detected in prior plasma tests, while the detection rate of T790M in subsequent tissue tests was 37% (25/68) when sensitizing mutations were detected in prior plasma tests (p = 0.004).

Because the sensitivity of plasma EGFR test for T790M is low, follow-up tissue or plasma tests are necessary. Presence or absence of a sensitizing mutation in the initial plasma tests can be used to determine which samples (tissue or plasma) should be submitted for further testing.

Keywords: Non-small cell lung cancer, Epidermal growth factor receptor (EGFR), Circulating tumor DNA (ctDNA), Repeat tests, Acquired resistance
CONSOLIDATIVE HIGH-DOSE RADIOTHERAPY FOR OLIGOMETASTATIC NON-SMALL CELL LUNG CANCER

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1Department of Radiation Oncology, Korea University Guro Hospital, Korea University College Of Medicine, Seoul, Republic Of Korea,
2Department of Internal Medicine, Korea University Guro Hospital, Korea University College Of Medicine, Seoul, Republic Of Korea

Several previous studies have demonstrated the survival benefit of local radiotherapy for oligometastatic non-small cell lung cancer (NSCLC) and phase III trials are ongoing. In this background, we aimed to evaluate the impact of the consolidative high-dose radiotherapy on local control rates and survival outcomes in patients with oligometastatic NSCLC.

We retrospectively reviewed the medical records of 33 patients with oligometastatic NSCLC who received consolidative high-dose local radiotherapy at Korea University Guro Hospital between March 2015 and March 2020. In the current study, we defined the oligometastasis as having 1 to 3 metastatic lesions at the time of diagnosis. All patients received either stereotactic ablative radiotherapy (SABR, 16 patients, 48.5%) or intensity-modulated radiotherapy (IMRT, 17 patients, 51.5%). Revised Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (Version 1.1) were used to evaluate tumor response.

The median follow-up time was 31 months (range, 5 to 77 months). There were 11 patients who developed recurrence (33.3%). Distant metastasis was the most common pattern of recurrence (9/11 patients, 81.8%). Distant metastasis alone, locoregional recurrence alone, and both occurred in eight, two, and one patients, respectively. The most common site of distant metastasis was the brain (four patients), followed by the bone (three patients). In terms of radiotherapy, in-field local recurrence occurred in only one patient. For all patients, the overall 2-year disease-free survival (DFS) and overall survival (OS) rates were 80.7% and 92.7%, respectively. The overall 3-year DFS and OS rates were 65.7% and 88.3%, respectively. The median DFS time was 60 months after systemic treatment and median OS time was not reached.

Consolidative high-dose radiotherapy to primary and metastatic sites could improve local control rates with acceptable treatment-related toxicities and achieve long-term survival in NSCLC patients with a limited number of metastatic sites.

Keywords: Non-small cell lung cancer, Oligometastasis, Radiotherapy, Survivals
LUNG CANCER IN THE PREGNANT WOMAN: TO TREAT OR NOT TO TREAT, THAT IS THE QUESTION

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Department of Biology, Universitas Gadjah Mada

Lung cancer (LC) is the most common cancer in the world. Lung cancer in pregnancy is a rare situation; however, it is increasingly reported in the past two decades. The association might be more encountered in the coming years due to the rising trends of cigarette smoking among young women and tendency to delay pregnancy to later in life. Approximately 1 per 1,000-1,500 pregnancies is complicated by maternal malignancies. Metastatic involvement of the products of conception is a rare event. The aim of this study is to raise awareness about lung cancer in pregnancy.

Data obtained from secondary data on 11 articles journal evaluated by searching in PubMed, EMBASE, and the Cochrane Library database that have been carried out in the last 10 years (2010-2020).

The result showed the association might be more encountered in the coming years due to the rising trends of cigarette smoking among young women and tendency to delay pregnancy to later in life. Patients had poor post-partum outcome with less than one-forth alive at 1 year following delivery. There was a high incidence of metastases to the products of conception reaching 26%. Eight patients were treated with systemic therapies during the course of gestation with normal fetal outcome and no evidence of fetal or placental metastases.

It can be concluded that counseling of these patients is very important. Apart from the clinical conflict they pose, some ethical aspects should be taken in consideration. The poor maternal prognosis should be discussed and the patient’s autonomy should be respected to decide whether she wants to keep the pregnancy or not.

Keywords: Lung cancer, Pregnant woman, Pregnancy
A RARE CASE OF LUNG ADENOCARCINOMA HARBORING V600 DELETION MUTATION

Heae Surning Park
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BRAF inhibitor was approved for lung adenocarcinoma patients with BRAF V600E mutation. In Korea, PCR-based method was generally used to detect BRAF V600E mutation. However, this test cannot detect non-V600E mutation. Herein, we present a rare case of lung adenocarcinoma with V600 deletion mutation.

79 year old female was referred due to chest CT abnormality. She had a cough for one month and medication for hypertension and diabetes. Chest CT showed an unchanged about 1.6 cm sized semisolid nodule in LLL (#187) with suspicious enhancement. Diagnostic wedge resection of the LLL with following lobectomy with mediastinal LN dissection was done. Gross exam revealed an ill-defined subsolid mass measuring 1.5 x 1.1 cm. Pathological exam showed papillary predominant adenocarcinoma without lymph node metastasis (pT1bN0).

PCR-based EGFR mutation and ROS1 rt-PCR tests were negative and ALK companion diagnostic test was also negative. PCR-based BRAF test (PANAgene) was positive and direct sequencing of BRAF gene revealed BRAF V600 deletion mutation.

PCR-based Braf test should be confirmed by direct sequencing in lung adenocarcinoma.

Keywords: Lung, Adenocarcinoma, Braf
CYTOKINE PROFILE OF EGFR WILD AND MUTANT TYPE LUNG ADENOCARCINOMA CELL LINES AFTER DIFFERENT RADIATION DOSES

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Immunologic aspect of radiation response is not well known. There would be differences in cytokine levels according to radiation sensitivity. We evaluated the cell survival and cytokine levels of lung adenocarcinoma cell lines and normal lung cell lines at different time and radiation fraction size.

Three different lung cell lines were used including BEAS-2B (human bronchial epithelial cell line), A549 (EGFR wild type lung adenocarcinoma cell line), and PC9 (EGFR mutant type lung adenocarcinoma cell line). The cell lines were irradiated with 2 and 8 Gy using 6MV x-rays from Elekta InfinityTM linear accelerator at dose rate of 2 Gy/min. Cell viability assay was done using cell counting kit-5 at 6, 24, 48 and 72 hour after radiation. We analyzed a cytokine profile of irradiated conditioned media at 6, 24, 48 and 72 hour after radiation. Concentration of interleukin (IL)-1ß, 2, 6, 10, 12, 22, 23, interferon (IFN)-γ and tumor necrosis factor (TNF)-a was analyzed using Multiplex bead assay and Real time PCR.

Cell viability decreased after radiation and the changes were larger in A549 cells than PC9 cells. The degree of change in cell viability showed the difference according to the radiation fraction size in the A549 cells and PC9 cells, however normal lung cell line did not show the difference. A549 cells was more sensitive to radiation fraction size. TNFa increased after radiation in all cells and the change differed according to radiation fraction size in PC9 cells. IL-10 and IL-1ß did not show the difference through the time, cell line and radiation fraction size. IL-6 showed the tendency of increase in all cell lines, however, there was no difference according to radiation fraction size. IL2, 12, 22 and 23 increased through the time in A549 cells and the changes were largest between 48 and 72 h after radiation.

EGFR wild type adenocarcinoma was more sensitive to the radiation fraction size than EGFR mutant adenocarcinoma cell line. Cytokines showed a variety of patterns of change, and their patterns varied depending on lung cancer cell lines and radiation fraction size. The mechanism for various cytokine involvement regarding to cell viability
warrant further investigation.

**Keywords:** Lung cancer, Cytokine, Radiation
OVERCOMING ACQUIRED RESISTANCE TO EGFR INHIBITOR THROUGH MODULATION OF ERK

Bo Mi Ku, Jong-Mu Sun, Se-Hoon Lee, Jin Seok Ahn, Keunchil Park, Myung-Ju Ahn
Department of Hematology-Oncology, Samsung Medical Center,

EGFR mutant-selective tyrosine kinase inhibitors (TKI) are clinically effective in non-small cell lung cancer (NSCLC). However, acquired resistance can occur by reactivating ERK. Therefore, targeting ERK may alternative therapeutic strategy to overcome acquired resistance. However, the function of specific ERK inhibitor is not well elucidated in acquired resistance model.

ERK activation in NSCLC patients with acquired resistance was evaluated by immunohistochemistry using FFPE tissue. Erlotinib- and osimertinib-resistant cells were used to test efficacy of ERK inhibitor. Drug effects on resistant cells were evaluated with cell viability assay, colony formation assay, western blotting, cell cycle analysis in vitro and xenografts in vivo.

In retrospective analysis of paired (pre- and post-treatment) biopsy samples from EGFR-TKI treated patients, ERK activation level was significantly higher in post-treatment biopsy compared with pre-treatment sample. The specific ERK inhibitor treatment inhibited tumor cell growth and cell cycle in cells harboring acquired resistance to EGFR-TKI. In addition, the combination of ERK inhibitor with EGFR-TKIs synergistically decreased the growth of resistant cells with enhanced induction of cell death.

Targeting ERK using specific ERK inhibitor is an effective strategy to overcome acquired resistance to EGFR inhibitor.

Keywords: Non-small cell lung cancer, Acquired resistance, ERK inhibitor
TUMOR-ASSOCIATED IMMUNE CELL PROFILING REVEALS DISTINCT IMMUNE CHECKPOINT INHIBITOR OUTCOMES IN ADVANCED NON-SMALL CELL LUNG CANCER

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Immune checkpoint inhibitors are a significant advance to the treatment of advanced non-small cell lung cancer (NSCLC). This study aimed to evaluate the profiles of tumor-associated immune cells in tumor microenvironment and identify determinants associated with response in patients with NSCLC treated with PD-1 blockade.

Tumor biopsy specimens from 100 NSCLC patients treated with pembrolizumab or nivolumab were analyzed. The density profile of T cells, B cells, and macrophages were analyzed using multiplex immunohistochemistry and image analysis.

In our cohort, patients were treated with pembrolizumab (n = 43, 43.0%) or nivolumab (n = 57, 57.0%). The best response in this cohort was partial response (PR) in 28 patients (28.0%), stable disease (SD) in 14 patients (14.0%), and progressive disease (PD) in 58 patients (58.0%). Patients with PR and SD > 6 months were classified as durable clinical benefit (DCB; n = 30, 30.0%), while patients with SD = 6 months and PD were classified as non-durable clinical benefit (NDCB; n = 70, 70.0%). Median progression-free survival (PFS) of DCB and NDCB were 11.3 months (HR 0.22, 95% CI 0.15-0.34) and 1.2 months (HR 4.45, 95% CI 2.95-6.73), respectively. Immune cell distribution was heterogeneous and more abundant in stroma than tumor regions. Most dominant immune cell type was T cells. The ratio of tumor/stroma region of T cell (CD8 T and CD4 T), B cell, and macrophage was significantly higher in patient with durable clinical benefit (DCB) than others. Patients with DCB showed significantly higher PD-L1 expression. In Chi-square test, intratumoral CD8 T cell density was significantly associated with intratumoral Treg density, but not B cell or macrophage.

A high intratumoral immune cell density shows positive predictive and prognostic indicator for patients with advanced NSCLC regardless of PD-L1 expression.

Keywords: Non-small cell lung cancer, Tumor-associated immune cells, Tumor microenvironment, Immune checkpoint inhibitor
IMPACT OF PRE-TREATMENT AXL EXPRESSION ON EGFR-TKI EFFICACY IN PATIENTS WITH NON-SMALL CELL LUNG CANCER WITH EGFR MUTATION

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EGFR-tyrosine kinase inhibitors (TKIs) have marked efficacy in patients with EGFR-mutated non-small cell lung cancer (NSCLC). However, some patients show intrinsic resistance and an insufficient response to EGFR-TKIs. Increased expression of the anexelekto (AXL) protein in tumors is reported to be associated with poor prognosis in patients with several types of cancer. We previously reported the crucial role of the AXL pathway in the intrinsic resistance to EGFR-TKIs in EGFR-mutated NSCLC cells. However, the relationship between AXL expression in tumors and the therapeutic efficacy of EGFR-TKIs remains unknown.

We retrospectively enrolled 74 patients with advanced or relapsed NSCLC with EGFR-activating mutations from nine institutions in Japan. All patients were administered gefitinib, erlotinib, afatinib or osimertinib as the first-line treatment between May 2008 and March 2019.

Fifty-four (72.0%) patients were female. The median age of patients was 67.5 years (43–88). The EGFR-activating mutations were deletion in exon 19 in 40 (53.3%) patients; L858R missense mutation in exon 21 in 29 (38.7%); and others in 6 (8.0%). High (3+), intermediate (2+), low (1+), and no (0) pre-treatment expression of AXL in tumors was observed in 12 (16.0%), 13 (17.3%), 35 (46.7%) and 15 (20.0%) patients, respectively. The objective response rate following EGFR-TKI treatment in the patients with low AXL expressions (0 and 1+) was high, compared with that with high AXL expressions (2+ and 3+) (83.7% vs. 64.0%, p = 0.080). Interestingly, a longer progression-free survival was observed in the patients with low AXL expressions than that with high AXL expressions in patients with L858R mutations (p = 0.013), but not deletion in exon 19 (p = 0.616).

Pre-treatment AXL expression in tumors may be a promising predictor of EGFR-TKIs treatment efficacy in patients with EGFR-mutated NSCLC, especially L858R mutations.

Keywords: Non-small cell lung cancer, EGFR, EGFR-TKI, AXL, Resistance, Biomarker
DIAGNOSTIC EGFR MUTATIONS IN NON SMALL CELL LUNG CANCER WITH SPECIMENS OF BODY CAVITY FLUIDS

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Based on the nature of the body fluid samples, there are the presence of suspended DNA fragments that help to make an EGFR mutation diagnosis. From this principle, we conduct research with the following objectives:

1. Investigate the positive rate of EGFR mutations in body fluid samples.
2. Comparison with the same patient result diagnosed with EGFR mutation in paraffin block histological specimens.
3. Partially surveying the diagnostic value of EGFR mutations in body fluid samples.

Retrospective, descriptive statistics cross-section. Cases of NSCLC are diagnosed with EGFR mutations by paraffin block histological specimens with Cobas Test EGFR Version 1 and body fluid samples (pleural fluid, pericardial fluid, peritoneal fluid, cerebrospinal fluid) with Cobas Test EGFR Version 2.

- Results of EGFR mutation diagnosis on paraffin block histology: (+) 49 cases # 41.88%, equivalent to statistics in the Vietnam and the World (Asia). The majority are still two types of drug-sensitive mutants TKIs: Exon 19 Deletion and Exon 21 L858R (53% and 23%).
- Results of diagnosis of EGFR mutation in samples of body cavity fluids: Most samples of body cavity performing diagnosis of EGFR mutation were pleural fluid (91 cases # 77.77%). The highest rate of detection of mutations in pleural and cerebrospinal fluid samples (29.67% & 83.33%). Comparing the rate of detection of EGFR mutation in body fluid samples (35/117 cases # 29.91%) with the statistically lower rate of detection in histological samples (29.91% ↔ 41.88% with P = 0.0125). Compared with other studies in the world, the majority of studies have higher results than those at Pham Ngoc Thach Hospital.

Investigation of EGFR mutations in body cavity fluids, a positive result of 29.91% shows that this is a new application step to help diagnose EGFR mutations in cases where histological specimens are difficult to obtain. Especially in cases of NSCLC progresses. The ability to detect EGFR mutations was highest in pleural fluid (29.67%) and cerebrospinal fluid (83.33%). It is necessary to improve the technique of performing EGFR mutant diagnosis in body cavity samples with the more sensitive methods: Droplet Digital PCR, Next Generation Sequencing ect.

Keywords: FFPE: Formalin-Fixed Paraffin-Embedded Tissue, Body cavity fluids, Cell Free DNA
ANALYSIS OF THE IMPACT OF CHEMOTHERAPY IN LUNG CANCER PATIENTS IN INDONESIA: LITERATURE REVIEW

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Lung cancer in Indonesia is the first malignant cancer for men. This is caused by smoking and air pollution. This study analyzed the effects of chemotherapy on lung patients in Indonesia.

This study reviews several journals that have been published from 2000-2019 on chemotherapy in Indonesia.

The results show that there are two chemotherapy used in Indonesia, namely Cisplatin-Docexatel (DC) and Cisplatin-Etoposide (EC). Between these two types of DC chemotherapy’s is better than EC chemotherapy’s. It turns out that the impact of chemotherapy does not produce pain as conveyed by this analysis, this is because the pain that can arise may not be from the equipment used but from the pain suffered.

So, lung cancer patients in Indonesia are recommended to use Cisplatin-Docexatel because it does not cause pain.

Keywords: Lung cancer, EC, DC, Indonesia, Chemotherapy
ACQUIRED RESISTANCE MECHANISMS OF Osimertinib IN PATIENTS WITH DE NOVO EGFR T790M-MUTANT NON-SMALL CELL LUNG CANCER (NSCLC)

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Background: De novo epidermal growth factor receptor (EGFR) T790M mutation is rarely observed (0.8~2%) in EGFR-mutant non-small cell lung cancer (NSCLC). Although osimertinib has been proved as an effective treatment for EGFR T790M-positive NSCLC, osimertinib resistance mechanisms have not been well understood in NSCLC with de novo EGFR T790M mutation.

Methods: We analyzed paired tumor and blood samples from three NSCLC patients with de novo EGFR T790M/L858R who received osimertinib. The fresh tumor or blood samples were obtained before and after treatment with osimertinib. Whole exome sequencing, targeted sequencing, fluorescence in situ hybridization (FISH), and droplet digital PCR (ddPCR) were performed to evaluate the genetic alterations related to osimertinib resistance. The oncogenicity of genetic alterations identified in patient samples were reproduced using Ba/F3 system and NCI-H1975 cell line. Osimertinib resistance mechanisms caused by the specific genetic alteration were confirmed through in vitro cell viability assays and Western blots in the genetically engineered NCI-H1975 cell line.

Results: The clonal mammalian target of rapamycin (MTOR) L1433S mutation, MET amplification with MAX dimerization protein MGA (MGA) V124D mutation, and EGFR C797S mutation were identified as acquired resistance mechanisms to osimertinib in LC1, LC2, and LC3 patients, respectively. The oncogenicity of MTOR L1433S was confirmed using Ba/F3 model and osimertinib resistance was observed in NCI-H1975 cell line harboring MTOR L1433S mutation. Osimertinib resistance caused by MTOR L1433S mutation was abrogated by osimertinib in combination with mTOR inhibitors.

Conclusion: MET amplification, EGFR C797S mutation, and MTOR L1433S mutation were identified as resistance mechanisms of osimertinib in de novo EGFR T790M/L858R-mutant NSCLC patients. De novo EGFR T790M/L858R-mutant NSCLC cells with acquired MTOR L1433S mutation were inhibited by osimertinib plus mTOR inhibitors, suggesting a novel therapeutic strategy.

Keywords: NSCLC, De novo EGFR T790M, Osimertinib, Resistant mechanism, MTOR L1433S
LUNG CANCER IN INDONESIA: HOW INDONESIA MEDICAL SCIENCES FIGHT WITH THIS ISSUE?

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According to the data of the Indonesian Lung Association (PDPI) the number of lung cancer patients who visited the national respiratory cancer increased nearly 10 fold compared to 15 years ago. Besides the highest cancer in Indonesia is lung cancer in third position 8.6% (males and females) (Data produced by WHO 2018). How do health/cancer experts in Indonesia deal with lung cancer which continues to increase from year to year? What are they doing?

This study uses an electronic database as a method by reviewing several recent articles that discuss an issue in the 2000s.

There are several research results from Indonesian medical scientists regarding lung cancer and their actions. Firstly, lung cancer is often found in men in old and middle age with the main complaints of shortness of breath (58.1%) and pain (32.5%). The action taken was to perform surgery in 9 cases, radiotherapy in 17 cases and chemotherapy in 5 cases. Secondly, patients with large lung cancer (adenomarcinoma) have a prognosis for a one-year mortality rate, especially for underweight patients who have a higher risk of death. Thirdly, the smoking habit of Indonesians with > 20 cigarettes per day can increase the risk of malignant lung cancer.

The high mortality rate and lung cancer in Indonesia causes more effort to reduce the mortality rate by campaigning for things related to the dangers of smoking and so on. The risk of death for old and middle age men does not rule out the possibility of attacking women and children.

Keywords: Lung cancer, Medical scientist, Indonesia
IN VITRO ANTICANCER ACTIVITY OF ANDROGRAPHOLIDE DERIVATIVES IN NSCLC CELL LINES WITH VARIOUS K-RAS STATUS

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SRS07, SRS157, SRJ23 and SRJ09 are semisynthetic andrographolide (AGP) derivatives that was structurally modified from AGP to enhance anticancer activity. SRJ23 is the parent compound of SRS157 and SRJ09 is the parent compound of SRS07. The in vitro growth inhibitory properties of compounds were assessed in adenocarcinomic human alveolar basal epithelial cell cancer cell line (A549) with a KRAS point mutation substitution of G12S, however, it is unknown whether the semisynthetic compounds have a higher potency effect against KRAS mutation in A549.

These compounds were shown in a preliminary in vitro cell viability MTT assay measured by the half maximal inhibitory concentration (IC50)

The average IC50 of each compound including AGP are (AGP = 4.50 μM, SRJ23 = 3.25 μM, SRJ09 = 3.25 μM, SRS07 = 30.25 μM, SRS157 = 30.50 μM)

This shows that SRJ23 and SRJ09 have a higher potency compared to AGP that targets A549 with KRAS mutation of G12S, thus, opening possibilities for the derivatives to be applied in advanced stages in research

Keywords: Semisynthetic derivative, Andrographolide, IC50, Non small cell lung cancer cell line
GENETIC VARIANT OF BRD3 PREDICTS SURVIVAL OUTCOME AFTER SURGERY FOR NON-SMALL CELL LUNG CANCER

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Bromodomain and extraterminal domain (BET) proteins are epigenetic readers that regulate gene expression. We investigated whether regulatory solitary nucleotide polymorphisms (rSNPs) in BET genes are associated with clinical outcomes of non-small cell lung cancer (NSCLC).

The associations between 77 rSNPs in BET family genes and clinical outcomes were analyzed in the 773 surgically resected NSCLC (349 patients in the discovery and 424 patients in the validation cohorts).

Of the 77 rSNPs investigated, 11 rSNPs are associated with overall survival or disease free survival with P value less than 0.05 in the discovery cohort. Among 11 rSNPs, only one rSNP (BRD3 rs2506711C>T) was replicated with same direction as the discovery cohort, in the validation cohort. rs2506711C>T, located in the heterochromatin and repressed area, had strong linkage disequilibrium (D' and r2 = 0.98) with rs2427964C>T, predicted as active transcription start site. BRD3 rs2427964C>T was significantly associated with worse overall survival in the discovery, validation and combined analysis (under a recessive model, HR = 1.70, 95% CI = 1.11 – 2.61, P = 0.02; HR = 1.97, 95% CI = 1.18 – 3.28, P = 0.01; and HR = 1.92, 95% CI = 1.39 – 2.65, P = 8 × 10^-5, respectively). In the luciferase assay, BRD3 rs2427964T allele had a higher promoter activity than rs2427964C allele. TGCA data showed that patients with high BRD3 expression had worse prognosis than those with low BRD3 expression. In the functional study, knockdown of BRD3 with BRD3 specific siRNA has been shown to increase apoptosis rate and decrease proliferation in cancer cells. These results suggest that BRD3 rs2427964C>T increases BRD3 expression through an increase in promoter activity, which may have been shown as a poor prognosis for lung cancer.

We found that BRD3 rs2427964C>T was associated with poor survival outcome in NSCLC.

Keywords: BRD3, rs2427964, Epigenetics, NSCLC, Survival outcome, BET, Polymorphisms
EXPRESSIONS OF BIOMARKERS OF MALIGNANT PLEURAL MESOTHELIOMA AT PHAM NGOC THACH HOSPITAL, VIETNAM IN 5 YEARS FROM 2015-2019

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The survey of the biomarkers of MPM partly aims to build a standard in diagnosis and anticipate upcoming treatment trends for this malignant tumors. In Vietnam, currently there are no extensive studies on the biomarkers of MPM in large quantities. We carry out research on MPM biomarkers for the following objectives:

1. Investigation of diagnostic epidemiological markers and diagnostic immunohistochemistry biomarkers in diagnostic MPM.
2. Investigation of gene mutation expressions and PD-L1 expressions in MPM.
3. Application in diagnostic evaluation and future treatment trends for MPM.

Retrospective, descriptive statistics with cross-section. Investigation of manifestations: epidemiology, diagnostic immunohistochemistry, gene driver expressions, and immune check point PD-L1 expressions in MPM.

a. There is evidence of presentative asbestos bodies (16.93%) and SV-40 (7.26%).

b. Calretinin, Glut-1, XiAP and WT-1 immunohistochemistry markers [Positive ratios: 105 cases (84.68%), 102 cases (82.26%), 103 cases (83.06%) and 116 cases (93.54%)] have been the highest expressions in the cases of MPM and has the best value in diagnosing MPM.

c. The most important gene expression have been recognized: p16 Deletion and BAP1 [Positive rates: 8 cases (6.45%) and 15 cases (12.09%)]. There is possibility of application in targeted treatment.

d. There is a positive PD-L1 ratio with two markers 22C3 and SP263 [Positive rate: 17 cases (13.71%) and 25 cases (20.16%)]. This also leads to applicability for immunotherapy for MPM.

Through a survey of biomarkers in 124 cases MPM at Pham Ngoc Thach Hospital from 2015-2019 we have brought the following statements:

- For diagnosis: There is evidence of presence of asbestos body and SV-40 and the IHC markers of Calretinin, Glut-1 and WT-1 have been the highest expressions in the cases of MPM and have been the best values in epidemiological diagnosis and positive diagnosis of MPM.
- For treatment: The most important gene expressions have been p16 Deletion and BAP1 and a positive PD-L1 ratio with two markers 22C3 and SP263. This also leads to the possibility of targeted application and immunotherapy for MPM.

Keywords: Malignant Pleural Mesothelioma, Epithelioid MPM, Sarcomatoid MPM, Biphasic MPM, Well-differentiated Papillary MPM, Deletion p16, BAP1: BRCA1 associated protein-1 (ubiquitin carboxy-terminal hydrolase)
EFFECT PALLIATIVE CARE ON QUALITY OF LIFE FOR LUNG CANCER PATIENTS: A LITERATURE OF REVIEW

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One of the leading causes of cancer death worldwide is lung cancer. It is a very deadly disease and most patients give up within a short period of time although over the last few decades, the survival rates for many types of cancer have increased. A number of treatment options are available depending on the stage of the lung cancer. However, many patients give up on their lives. So that palliative care is a solution to strengthen his self-confidence and relieve patient suffering.

This study aims to analyze various of the quality of life of patients after using palliative care measures. This study used electronic database which published from 2001-2019. Ten articles were selected based on the articles using research that made the research object of non-small cell lung cancer (NSCLC) patients

Anxiety, depression, mood, Pain, Insomnia, social and role, and pulmonary function of NSCLC patients are indicators of palliative care. On an average of ten articles, indicators of social and role function, Anxiety, Depression and Pulmonary Function are getting better with palliative care compared to standards care.

So it can be indicated that palliative care is highly recommended for patients, especially those who think that their age is not long and feel comfortable until the end of their lives.

Keywords: Palliative Care, NSCLC, Quality of life, Mood
PREDICTION OF DELAYED PNEUMOTHORAX USING LUNG ULTRASOUND AFTER TRANSTHORACIC NEEDLE BIOPSY

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The use of lung ultrasound can evaluate various thoracic disease and acute dyspnea cause in critical care patients. Lung ultrasound has a higher sensitivity than chest radiography for the detection of a pneumothorax. The aim of this study is to perform comparison of lung ultrasound and chest x-ray for the early diagnosis of delayed pneumothorax.

Of the 56 patients prospectively included in this study, 37 CT-guided, and 16 Electromagnetic-guided lung biopsies were performed from March 2020 to July 2020. The bedside initial ultrasound was performed in upper BLUE point and lower BLUE point before the transthoracic needle biopsy procedure. A follow-up chest radiograph and lung ultrasound were obtained immediately, and 3h after the biopsy procedure.

The mean age 69±11.9 years, and 63.6% of the patients was male. Pneumothorax developed immediately after transthoracic needle biopsy procedure was 10 of the 53 patients (18.9%), and 4 of the 53 (7.5%) patients delayed pneumothorax developed. 1 of 4 patients with delayed pneumothorax was not detected on lung ultrasound and chest radiography obtained immediately and 3h after lung biopsy. He developed a delayed pneumothorax the next day. Of 4 patients with delayed pneumothorax, 3 patients was detected loss of lung sliding and a-lines on lung ultrasound immediately after the procedure but not detected a pneumothorax on chest radiography. Their pneumothorax were found follow-up chest radiography after 3hours.

The sensitivity of lung ultrasound to the early detection of delayed pneumothorax was 75% in this study. Our results suggest that Delayed pneumothorax does not develop on chest x-ray 2 to 4hrs after transthoracic needle biopsy, but there is an occult pneumothorax which was not found on chest radiography immediately after the procedure. To perform lung ultrasound can help the early diagnosis of delayed pneumothorax developed after the transthoracic needle biopsy.

Keywords: Delayed pneumothorax, Lung ultrasound
To investigate association non smoking women and lung cancer.

The method used in this study is literature review by taking journals that have been published online consisting of Indonesian and English journals. The criteria for sampling were in accordance with the key words, namely lung cancer, non smoking women. The inclusion criteria were primary research, English, Indonesian, and publications in the last 10 years. A total of 933,087 articles were found based on keywords and continued with screening based on inclusion criteria, and a total of 995 articles met the inclusion criteria. Subsequently, an analysis using the JBI tool was performed, including components of objectives, methods, samples and settings, criteria and results. There are 20 articles as the final article for further analysis.

The relationship between cigarette smoking and lung cancer was statistically significant although only a small proportion of female patients had smoked. However, the risk of contracting cancer for non-smoking women appears to be associated with certain cooking practices, especially preparing meals in kitchens not equipped with a fume extractor at cooking age of 20-40 years. These factors and a history of pulmonary tuberculosis plus low consumption of fresh vegetables explained attributable risks for non-smoking.

Exposure to fumes from cooking oils, when not reduced by an extractor, may be an important factor in causing lung cancer in non-smoking.

Keywords: Lung cancer, Non smoking, Women
The N descriptors proposed by International Association for the Study of Lung Cancer have not been sufficiently validated. We aimed to evaluate the prognostic performance of the proposed N descriptors for clinical staging.

We included 1271 patients who had non-small cell lung cancer without distant metastasis from January 2010 to December 2014. Each patient’s clinical N stage was assigned to one of the seven categories: cN0, cN1a, cN1b, cN2a1, cN2a2, cN2b, and cN3. The 5-year overall survival rates were measured. The adjusted hazard ratios (HRs) and their 95% confidence intervals (CIs) were estimated using a multivariable Cox proportional hazard model. The current and proposed cN stages were compared in terms of the overall prognostic performance.

The 5-year overall survival rates were 77.3%, 53.7%, 36.0%, 29.2%, 34.4%, 18.0%, and 12.4% for the stages cN0, cN1a, cN1b, cN2a1, cN2a2, cN2b, and cN3, respectively. There were no significant prognostic differences between the cN1b and cN1a (HR, 1.13; 95% CI, 0.61–2.09, p = 0.71) and between cN2a2 and cN2a1 (HR, 0.98; 95% CI, 0.61–1.56, p = 0.93) stages. cN2b was related to a worse prognosis than cN2a (HR, 1.53; 95% CI, 1.06–2.22, p = 0.02). The C-indexes were 0.805 and 0.798 for the current and proposed cN stages, respectively (p > 0.99).

A survival difference was observed between the single- and multi-station involvement in cN2 disease. The number of involved lymph node stations in cN1 disease and presence of skip metastasis did not show prominent survival differences.

Keywords: Cancer staging, N category, Lung cancer, Survival analysis
COLLATERAL EFFECTS OF THE CORONAVIRUS DISEASE 2019 PANDEMIC ON LUNG CANCER DIAGNOSIS IN KOREA

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Background: The COVID-19 pandemic is predicted to significantly affect patients with lung cancer, owing to its rapid progression and high mortality. Studies on lung cancer diagnosis and treatment during an epidemic are lacking. We analyzed the impact of COVID-19 on lung cancer diagnosis in Korea, where lung cancer incidence continues to rise.

Method: The number of newly diagnosed lung cancer cases in three university-affiliated hospitals during the pandemic and their clinical features were compared with lung cancer cases diagnosed during the same period in the past three years. The effectiveness of measures taken by the study hospitals to prevent nosocomial transmission was reviewed.

Results: Between February and June during 2017–2020, 612 patients with lung cancer were diagnosed. During the pandemic, the number of patients who sought consultation at the division of pulmonology of study hospitals dropped by 16% from the previous year. Responding to the pandemic, the involved hospitals created physically isolated triage areas for patients with acute respiratory infection symptoms. Wide-range screening and preventive measures were implemented, thus minimizing delay in lung cancer diagnosis. No patients acquired COVID-19 due to hospital exposure. The proportion of patients with stage III–IV non-small-cell lung cancer (NSCLC) significantly increased (2020: 74.7% vs. 2017: 57.9%, 2018: 66.7%, 2019: 62.7%, p=0.011). The number of lung cancers diagnosed during this period and the previous year remained the same.

Conclusion: The proportion of patients with advanced NSCLC increased during the COVID-19 pandemic.

Keywords: COVID-19, Epidemic, Lung cancer, Korea
DOSE-ESCALATED RADIOTHERAPY FOR LIMITED-DISEASE SMALL CELL LUNG CANCER

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Radiotherapy-dose escalation of definitive concurrent chemoradiotherapy (CCRT) for limited-disease small cell lung cancer (LDSCLC) is under the investigation to improve local tumor control. We evaluated the clinical outcome of dose-escalated radiotherapy to find an optimal once a day schedule.

Patients treated with definitive CCRT for LDSCLC between Jan 2018 and Dec 2019 were retrospectively reviewed. Standard radiotherapy dose was 52.5 Gy/25fx [BED 63.5Gy10], but total doses of 60 Gy/30fx [BED 72.0Gy10] or 60.9 Gy/21fx [BED 73.7Gy10] were delivered in some patients by physician’s decision. The institutional standard chemotherapy regimen was etoposide with CDDP given as 4 cycles. In-field progression (IFP) was defined as local progression within the designated radiotherapy field and survival was calculated from the date of diagnosis. Adverse events were graded upon CTCAE version 5.0.

A total of 41 patients were evaluated and the median age was 63 years (range, 47-78). Most patients were male (36/41, 88%) and had a smoking history (35/41, 85%). All patients were in stage II-III (American Joint Committee on Cancer, 8th edition). The Median follow-up time was 14.5 months (range 6.0-30.7). The number of each dose group was 19 of standard dose and 22 of escalated dose [7 of 60 Gy/30fx, 15 of 60.9 Gy/29fx]. Patients who showed progression in the radiotherapy field as the first failure site were 8 (42.1%) in the standard-dose group and 4 (28.1%) in the escalated group (p=0.093). The 1-year IFP-free survival rate as the first failure site was 70.6% in the standard-dose group versus 79.9% (p=0.229) in the escalated group. The 1-year overall survival (OS) was 83.9% in the standard group and 90.4% (p=0.330) in the escalated group. There was no difference in the incidence of acute or late severe adverse events over grade 3.

In-field progression as the first site failure tended to decrease in the dose-escalated radiotherapy group, but could not reach statistical difference. Escalated radiotherapy over 60 Gy did not lead to increased adverse events. Further investigation with more patients and follow-up time is necessary to conclude effects on local control of LDSCLC.

Keywords: Dose, Escalation, Radiotherapy
PROSPECTIVE STUDY OF HYPOFRACTIONATED PROTON THERAPY FOR INOPERABLE EARLY STAGE LUNG CANCER; PRELIMINARY RESULTS

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We present the preliminary results of hypofractionated proton beam therapy (PBT) for early stage lung cancer, which was unfit for surgical resection or stereotactic body radiotherapy.

From March 2018 to January 2020, we prospectively enrolled 18 patients with lung cancer. Inclusion criteria were cT1-3N0 lung cancer according to the 8th American Joint Committee on Cancer staging manual. The prescribed dose was 64 Cobalt Gray Equivalent in 8 fractions. PBT was delivered with the proton therapy system at our institution (Sumitomo, Japan). Primary endpoint was local control, and secondary endpoints were overall survival, quality of life, and grade ≥3 toxicity according to CTCAE v5.0.

The median age was 73.5 years (range, 57-84). Most of the patients were male (94.4%). Ten (55.6%) patients had underlying lung disease; idiopathic pulmonary fibrosis (IPF) in 6 (33.3%), combined pulmonary fibrosis and emphysema in 2 (11.1%), and chronic obstructive pulmonary disease in 2 (11.1%) patients. Clinical T-stages were T1 in 8 (44.4%), T2 in 6 (33.3%), and T3 in 4 (22.3%) patients. Adenocarcinoma and squamous cell carcinoma were diagnosed in 8 (44.4%) and 5 (27.8%) patients, respectively. The remaining 5 patients had histologically unproven lung cancer. The median tumor size and clinical target volume were 3.0 cm (range, 1.6-5.7 cm) and 66.9 cm\(^3\) (range, 28.7-321.8 cm\(^3\)), respectively. The median FEV1 and DLCO were 1.94L (range, 1.31-3.56L) and 60% (range, 28-102%), respectively. The median follow-up duration was 11.0 months (range, 1.1-32.1 months). During the follow-up period, 7 (38.9%) patients experienced disease progression after 4.5-29.0 months (median, 8.6 months); 2 with local progression, 1 with regional progression, 1 with local and regional progression, and 3 with local and distant progression. The sites of distant progression were pleura (n=2) and lung-to-lung metastasis (n=1). One-year local control and overall survival rate were 61.4%, and 88.2%, respectively. Grade 3 and 2 radiation pneumonitis were developed in 1 (5.6%) and 3 (16.7%) patients, respectively, while all the patients had underlying IPF. One patient experienced grade 3 dermatitis.

The preliminary result of local control following hypofractionated PBT for early stage lung cancer seems to be lower than expected. Severe toxicity was infrequent, but pulmonary toxicity in patients with IPF should be carefully monitored.

**Keywords:** Lung cancer, Proton therapy, Hypofractionation
This study is to report clinical outcomes and toxicities of salvage proton beam therapy (PBT) in patients with locoregionally recurrent non-small cell lung cancer (NSCLC). We retrospectively reviewed 53 patients who received salvage PBT for locoregionally recurrent NSCLC between January 2016 and December 2019. Target volume covered recurrent lesion with margin. The median gross tumor volume and clinical target volume (CTV) were 14.9 cm$^3$ (range, 2.3-759.5 cm$^3$) and 71.2 cm$^3$ (range, 13.3-1200.7 cm$^3$), respectively. The median prescribed dose was 64.0 Cobalt Gray Equivalent (CGE; range, 45.0-70.0 CGE). The median biologically equivalent dose at a/ß ratio of 10 Gy was 80.52 Gy10 (range, 58.5-115.2 Gy10). One-third (32.1%) received concurrent chemoradiotherapy (CCRT). The median age was 67 years (range, 44-86 years). There were 47 (88.7%) male and 6 (11.3%) female patients. Initial stages were I in 22 (41.5%), II in 8 (15.1%), and III in 23 (43.4%) patients. Initial treatments were surgery in 31 (58.5%), definitive CCRT in 12 (22.6%), definitive radiotherapy in 10 (18.9%) patients. Recurrent stages were I in 11 (20.8%), II in 11 (20.8%), III in 31 (58.4%) patients. Median disease-free interval (DFI) was 14 months (range, 3-112 months). Thirty-seven (69.8%) patients had previous radiotherapy history. Among of them, 18 (48.7%) patients had in-field recurrence, 12 (32.4%) patients had marginal field recurrence, and 7 (18.9%) patients had out-field recurrence. The median follow-up time after salvage PBT was 15.0 months (range, 3.5-49.3 months). During the follow-up period, 26 (49.1%) patients experienced disease progression. Local progression was developed in 11 (20.7%) patients, regional in 13 (24.5%) patients, and distant metastases in 14 (26.4%) patients. The median survival was 19.4 months, and 2-year overall survival (OS) rate was 79.8%. Two-year local control rate, progression-free survival rate, and distant metastasis-free survival rate was 66.8%, 39%, and 58.5%, respectively. Lower diffusing capacity for carbon monoxide (=80% vs. >80%, p=0.018), shorter DFI (=12 months vs. >12 months, p=0.013), and larger CTV (>80cc vs <=80cc, p=0.014) were associated with poor OS. Among them, only shorter DFI was an independent prognostic factor for OS in multivariate analysis (hazard ratio, 5.465; 95% confidence interval, 1.101-27.118, p=0.038). Grade 3 toxicities occurred in 7 patients (13.2%), esophagitis (n=2), dermatitis (n=3), pneumonitis (n=2), and bronchial obstruction (n=2). Salvage PBT for locoregionally recurrent NSCLC was effective, and treatment related toxicities were tolerable.

**Keywords:** Non-small cell lung carcinoma, Locoregional recurrence, Salvage therapy, Proton beam therapy
HOW TO MANAGE RADIOTHERAPY DURING COVID19 PANDEMIC?

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Department of Economic Faculty, Andalas University

Background: COVID-19 is currently still an unsolved problem. Indonesia is currently still in the top 3 of the most COVID-19 cases in ASEAN. Conditions that are not conducive today affect various aspects of human life today. The health sector is currently very busy in cases of COVID-19 which have occurred in almost every country. However, it should also be noted that health facilities are not only for COVID-19 patients, but there are other patients with various diseases waiting for safe, effective and efficient health services. Cancer patients who need several treatments in their treatment, one of the treatments done is radiotherapy. Therefore, it is necessary to pay attention to and prepare patient safety when doing radiotherapy during this pandemic.

Method: Literature review

Results: Radiotherapy during a pandemic needs to pay attention to several things to minimize the risk of being exposed to COVID-19. Radioteraphy patients must be determined by screening patients (patients with fever and no fever get different treatment) because patients who have fever and cough symptoms need to be aware that these patients are not exposed to COVID-19 before entering the radiotherapy room by observing for 7-10 days. Applying social distancing, room sterilization and radiotherapy machines using a disinfectant containing chlorine. Use of complete PPE for medical personnel to anticipate transmission of the corona virus, and masks for patients. In addition, patients exposed to COVID-19 need to be prohibited from canceling or stopping radiotheraphy. In severe pandemic conditions and difficult situations, radiotherapy is performed on patients in urgent conditions.

Conclusion: Radiotherapy procedures during the COVID-19 pandemic need to pay attention to health protocols and safety recommendations during the radiotherapy process to minimize the spread of covid19.

Keywords: Radiotherapy, COVID-19, Health protocol, Disinfectan
UPDATED RESULTS OF MODERATE-INTENSITY STEREOTACTIC BODY RADIATION THERAPY FOR ULTRA-CENTRAL LUNG TUMOR

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Stereotactic body radiation therapy (SBRT) for ultra-central (UC) lung tumors, generally defined as those abutting the proximal bronchial trees, is difficult due to concerns about serious toxicities. Therefore, our institution has performed moderate-intensity SBRT.

Patients with UC tumors underwent SBRT at a dose of 50 to 60 Gy in 10 fractions, with Dmax in the target volume not exceeding 110% of the prescribed dose. The primary outcomes were tumor response and overall survival (OS).

From January 2017 to August 2020, we treated fifteen patients who had been diagnosed with UC tumors. The median follow-up time was 12.7 months (range: 2.7–32.2). Eight of the fifteen patients (53.3%) showed a complete response (CR), four (26.7%) had a partial response (PR), one (6.7%) had stable disease (SD) and two (13.3%) showed progressive disease (PD); the response and disease control rates were 86.7% and 86.7%, respectively. One of the PD patients showed local progression at 20 months after SBRT and the other at 19 months. Twelve patients were alive with no evidence of disease or with controlled disease until the last follow-ups. One-year OS rate was 80.0%. Two patients died due to a non-RT cause at 3 months, 7 months after SBRT, respectively. One patient experienced grade 2 esophageal pain and another had grade 1 cough. One patient experienced massive hemoptysis 27 months after SBRT, which resulted in death. Otherwise, no grade 3 or higher toxicities were reported.

Moderate-intensity SBRT might aid in achieving good control of UC tumors. Future studies involving larger numbers of patients and longer follow-up times are warranted to confirm the safety, efficacy and feasibility.

Keywords: Stereotactic body radiotherapy, Ultra-central tumor, Feasibility, Radiotherapy
IMPACT OF IMMUNE CHECKPOINT GENE CD155 ALA67THR AND CD226 GLY307SER POLYMORPHISMS ON SMALL CELL LUNG CANCER CLINICAL OUTCOME

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1Department of Internal Medicine, School Of Medicine, Kyungpook National University, Kyungpook National University Hospital, Daegu, Republic Of Korea, 2Department of Biochemistry And Cell Biology, School Of Medicine, Kyungpook National University, Daegu, Republic Of Korea

This study was conducted to investigate the impact of genetic variants in immune checkpoint genes on the treatment outcome of patients with small cell lung cancer (SCLC).

Two hundred sixty-one patients who treated with platinum doublet were enrolled. Ninety-six polymorphisms in 33 immune checkpoint related genes were selected and their association with chemotherapy response and overall survival were analyzed.

Among polymorphisms studied, CD155 rs1058402G>A and CD226 rs763361C>T were significantly associated with the treatment outcome of SCLC. The rs1058402G>A had worse chemotherapy response and worse overall survival (under a dominant model, odds ratio [OR] = 0.52, 95% confidence interval [CI] = 0.27 – 0.99, P = 0.05; hazard ratio [HR] = 1.55, 95% CI = 1.12 – 2.14, P = 0.01, respectively). The rs763361C>T had better chemotherapy response and better overall survival (under a dominant model, OR = 2.03, 95% CI = 1.10 – 3.75, P = 0.02; HR = 0.69, 95% CI = 0.51 – 0.94, P = 0.02, respectively). When the rs1058402GA/AA and rs763361CC genotype were combined, the chemotherapy response and overall survival were significantly decreased as the number of bad genotypes increased (OR = 0.52, 95% CI = 0.33 – 0.81, Ptrend = 0.004; HR = 1.48, 95% CI = 1.19 – 1.84, Ptrend = 4 × 10^-4, respectively). CD155 rs1058402G>A and CD226 rs763361C>T are both non-synonymous mutations and change the protein sequence CD155 A67T and CD226 G307S, respectively. 3D structural model showed that CD155 A67T created new hydrogen bond and structural change on CD155. These changes resulted in extending the distance and losing the hydrogen bonds between CD155 and CD226, thus would weaken the binding activity of CD155/CD226.

CD155 rs1058402G>A (A67T) and CD226 rs763361C>T (G307S) may be useful for predicting the clinical outcome of SCLC after chemotherapy.

Keywords: Polymorphisms, CD155, CD226, SCLC, Clinical outcome
A CROSS-SECTIONAL STUDY ON TOBACCO CONSUMPTION PATTERN AMONG AUTO RICKSHAW DRIVERS IN CHENNAI CITY, TAMIL NADU, INDIA

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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 a 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.

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 analyzed using SPSS version 20. Chi-square test was used to test the significance between groups.

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.

Prevalence of tobacco duse 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: Lung Cancer, Tobacco, Consumption Pattern, Awareness, Cost
ANALYSIS RISK FACTORS AND CONSEQUENCES TOWARD LUNG CANCER DISEASE IN INDONESIA

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Lung cancer is all malignancies in the lung derived from bronchogenic carcinoma. According to 2018 Globally data, around 26,069 people in Indonesia die from lung cancer every year, with 30,023 new cases. The incidence of lung cancer is the most common in Indonesia, reaching 19.3\%. Risk factors such as gender, age, radiation exposure, family history, genetic, environment and smoking habits can affect of lung cancer. The purpose of this study was to analyze various risk factors and consequences of the incidence of lung cancer that occurred in Indonesia.

This study used electronic database as a method by reviewing some previous article published in the last five years, from 2014 to 2019. Literature review begins with topic selection, through several reputable published journals. Based on the similarity of the dependent variables there are various risk factors of lung cancer disease that occur in Indonesia, the result showed that there is a correlation between age, gender, genetics, environmental and smoking habits toward lung cancer. The gender factor was higher in male rather than female with the ratio 22.8\% and 14.2\%. Meanwhile age factor of Lung cancer patients mostly at \textgreater; 40 years (90.9\%). Risk factor bad habits had significant correlation on the probability of lung cancer, such as smoking habit. Previous research explained that, the main consequence of lung cancer is the inability of the immune system to defend the body from invasion of foreign matter. The smoking habit is also the main risk factors for cancer in Indonesia by donating 70\% of lung cancer deaths.

It can be concluded that in Indonesia, age, gender, genetic, environmental and smoking habits factors have significant correlation toward lung cancer disease. Early prevention is needed to minimize the consequences that occur in patients toward lung cancer, such as therapy is fast and precise and reducing the frequency of smoking habits.

Keywords: Consequences, Gender, Lung Cancer, Risk factors, Indonesia
Figure 1. The prevalence of cancer that occurs in Indonesia

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Source: Processed based on 2013 Basic Health Research Data, Indonesian Ministry of Health Research and Development Agency and Target Population Data, Pusdalin Ministry of Health RI
5년 동안 아이들은 얼마나 많이 자랐을까요.
보다 많은 야활자들과 가족들이 다시 평범한 일상을 누릴 수 있도록...

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- 전체 생존기간 중앙값(mOS): 비짐프로® 투여군 26.8개월, 게피티닙 투여군 19.1개월 (HR, 0.76; 95% CI, 0.582, 0.993, 2-sided p=0.044)  
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- 전체 생존기간 중앙값(mOS): 비짐프로® 투여군 26.8개월, 게피티닙 투여군 19.1개월 (HR, 0.76; 95% CI, 0.582, 0.993, 2-sided p=0.044)  
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7. VIZIMPRO® 약물
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9. VIZIMPRO® 약물
10. VIZIMPRO® 비침착

**Table 1:**

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<th>Condition</th>
<th>Frequency</th>
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<td>체중감소 (c)</td>
<td>33.3%</td>
<td>(85F30716)</td>
</tr>
<tr>
<td>피부건조 (b)</td>
<td>31.8%</td>
<td>(85F30716)</td>
</tr>
<tr>
<td>구내염 (a)</td>
<td>88.6%</td>
<td>(85F30716)</td>
</tr>
<tr>
<td>발진 (e)</td>
<td>79.2%</td>
<td>(85F30716)</td>
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<tr>
<td>손발톱 장애 (d)</td>
<td>71.8%</td>
<td>(85F30716)</td>
</tr>
<tr>
<td>근막염 (c)</td>
<td>65.5%</td>
<td>(85F30716)</td>
</tr>
<tr>
<td>피부건조 (b)</td>
<td>33.3%</td>
<td>(85F30716)</td>
</tr>
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</table>
새롭게 진단받은 ALK+NSCLC 환자에게 이제, 1일 1회 1정 [알론브릭®]으로 1차 치료가 가능합니다!

FOR YOUR ALK+ NSCLC PATIENTS
REDUCE THE RISK OF BRAIN METASTASES FROM TURNING ON

- Early separation of Kaplan Myer curves and 3 X longer mPFS vs. crizotinib (INV)
- Significant Increase in BIRC-Assessed intracranial PFS (4 X m i cPFS) evaluated in a rigorous clinical trial setting
- Long-Term safety profile with improvement in quality of life
- The Only approved first-line ALK inhibitor with one-pill, once-a-day dosing as of oct 2020

ALK, anaplastic lymphoma kinase; BIRC, blinded independent review committee; NSCLC, non-small cell lung cancer; PFS, progression-free survival.

PREScribing INFORMATION

PRECAUTIONS: Use only in patients with ALK gene mutation-positive advanced non-small cell lung cancer (NSCLC), who have failed crizotinib therapy or are intolerant to crizotinib. ALK testing should be performed on all patients with advanced NSCLC. Do not prescribe to women who are pregnant or breastfeeding. See patientinformation. See full prescribing information at www.PFIZER.com

REtention of Information: Use of this leaflet is to retain information for future discussions with healthcare professionals. This leaflet is not intended to be a substitute for professional medical advice, diagnosis or treatment. Follow the prescribing information before use and check all drug interactions. See Prescribing Information at www.PFIZER.com

REFERENCES: 1. sufficient data to support the claim, as per prescribing information. Available at: https://www.fda.gov/drugs/drug-approvals-and-d blues/ndacapphire

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The information on this material is intended for healthcare professionals only.
질병이 진행된 국소 진행성 또는 전이성 비소세포 폐암 환자의 치료. 다만 EGFR 또는 ALK 변이가 확인된 환자는 이 약을 투여하기 전에 이러한 변이에 대한 승인된 치료제를 ALK 유전자 변이가 있는 환자는 이 약을 투여하기 전에 표적치료제로 치료를 해야 한다.

치료로서 알부민 결합 파클리탁셀, 카보플라틴과의 병용요법 베바시주맙과의 병용요법 전이성 삼중음성 유방암 환자의 치료로서 알부민 결합 파클리탁셀과의 병용요법 1일에 투여한다. 추가로 알부민 결합 파클리탁셀은 제 8일, 15일에 투여한다. 주기 동안 이 약 1200mg을 정맥 점적주입 후 알부민 결합 파클리탁셀, 카보플라틴을 투여한다. 매 21일 간격의 주기 동안 이 약, 알부민 결합 파클리탁셀, 카보플라틴을 제 화학요법제 없이 이 약 1200mg을 정맥 점적 주입 후 베바시주맙을 투여한다.

병용요법 유도기: 병용요법 3주 간격으로 이 약 1200mg을 정맥 점적 주입 후 베바시주맙 15mg/kg를 투여한다.

식품의약품안전처에서 허가 받은 체외진단용 의료기기를 사용하여 종양침윤면역세포의 PD-L1 발현 상태를 확인 하여 환자를 선별해야 한다.

100mg/m2 알부민 결합 파클리탁셀을 투여한다. 매 28일 간격의 주기 동안 이 약을 제 1일, 15일에 투여하고 알부민 결합 파클리탁셀은 제 1일, 8일, 15일에 투여한다.

병용약제의 처방 정보를 확인한다. 같은 날에 병용 약제를 투여 시 이 약을 먼저 투여한다.

**이 약 1바이알(20mL) 중 유효성분: 아테졸리주맙 (별규) ‥‥‥ 1200mg ** 이 약 1바이알(14mL) 중 유효성분: 아테졸리주맙 (별규) ‥‥‥ 840mg

A PROVEN CONNECTION IN 1L ES-SCLC 티 сент리크 국내에서 유일하게 확장기 소세포폐암의 1차 치료제로 급여를 획득하였습니다. (2020년 9월 기준)

PRODUCT INFORMATION

**Atezolizumab (TECENTRIQ) + carbo/etop is a preferred immunotherapy/chemotherapy option (Category I) for first-line treatment of patients with ES-SCLC in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines)***

* NCCN makes no warranties of any kind whatsoever regarding their content, use, or application, and disclaims any responsibility for their application or use in any way. See the NCCN Guidelines for detailed recommendations.

**Category I: based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.**