



## Caring Ambassadors Lung Cancer Program Literature Review, May 2020

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### BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES

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#### [Lung CSC-derived Exosomal miR-210-3p Contributes to a Pro-Metastatic Phenotype in Lung Cancer by Targeting FGFR1](#)

Li Wang 1 2, Jun He 1, Haoyue Hu 1, Li Tu 1, Zhen Sun 2, Yanyang Liu 1, Feng Luo 1 J Cell Mol Med. 2020 May 12. doi: 10.1111/jcmm.15274. Online ahead of print.

Lung cancer has the highest mortality rate among human cancers, and the majority of deaths can be attributed to metastatic spread. Lung cancer stem cells (CSCs) are a component of the tumour microenvironment that contributes to this process. Exosomes are small membrane vesicles secreted by all types of cells that mediate cell interactions, including cancer metastasis. Here, we show that lung CSC-derived exosomes promote the migration and invasion of lung cancer cells, up-regulate expression levels of N-cadherin, vimentin, MMP-9 and MMP-1, and down-regulate E-cadherin expression. Moreover, we verified that these exosomes contribute to a pro-metastatic phenotype in lung cancer cells via miR-210-3p transfer. The results of bioinformatics analysis and dual-luciferase reporter assays further indicated that miR-210-3p may bind to fibroblast growth factor receptor-like 1 (FGFR1); silencing FGFR1 enhanced the metastatic ability of lung cancer cells, whereas overexpressing FGFR1 suppressed metastasis. Taken together, our results provide new insights into a potential molecular mechanism whereby lung CSC-derived exosomal miR-210-3p targets FGFR1 to promote lung cancer metastasis. FGFR1 may be a promising therapeutic target in lung cancer.

#### [Comparison of the Efficacy of EGFR Tyrosine Kinase Inhibitors Erlotinib and Low-dose Osimertinib on a PC-9-GFP EGFR Mutant Non-small-cell Lung Cancer Growing in the Brain of Nude Mice](#)

Yuki Katsuya 1 2, Kentaro Miyake 1 2, Takashi Higuchi 1 2, et al. In Vivo. May-Jun 2020;34(3):1027-1030. doi: 10.21873/invivo.11871.

**BACKGROUND/AIM:** Brain metastases are found in approximately 30% of patients with epidermal-growth-factor receptor (EGFR) mutant non-small cell lung cancer (NSCLC). We compared the efficacy of two EGFR-tyrosine kinase inhibitors (TKIs), erlotinib and osimertinib on a PC-9-GFP EGFR mutant NSCLC growing in the brain of nude mice. **MATERIALS AND METHODS:** The brain metastasis models were randomized into five groups and treated for 15 days: Control; 5 mg/kg erlotinib; 50 mg/kg erlotinib; 0.5 mg/kg osimertinib; 5 mg/kg osimertinib. Tumor volume was evaluated by non-invasive

fluorescence imaging. **RESULTS:** Only 5 mg/kg osimertinib, a low-dose compared to the clinically-equivalent dose, showed significant tumor regression compared to the control. **CONCLUSION:** This study strongly supports the high activity of osimertinib for intracranial lesions of EGFR-mutant NSCLC.

**Microarray Expression Profiling of Long Noncoding RNAs in the Progesterone-Treated Lung Cancer Cells** Mingxuan Xie 1 2 , Xiaoxiao Lu 3, Qiong Chen 1 2 J Gene Med. 2020 May 11;e3215. doi: 10.1002/jgm.3215. Online ahead of print.

**BACKGROUND:** The increasing incidence and unique biological features of lung cancer in women has prompted renewed interest in the role of sex hormones in this disease. We previously showed that progesterone (P4) inhibited lung cancer tumorigenesis and progression. Here, we investigated the effects of P4 on expression of long noncoding RNAs (lncRNAs) and target mRNAs in lung cancer cells.

**METHODS:** We performed high-throughput microarray and bioinformatics analysis to identify differentially expressed lncRNAs and mRNAs in the untreated and the P4-treated A549 human lung cancer cells. **RESULTS:** In total, 692 lncRNAs and 268 mRNAs were significantly differentially expressed in the P4-treated A549 cells compared to the untreated A549 cells (> 2-fold change,  $p < 0.05$ ). Of the lncRNAs, 82 and 610 were up-regulated and down-regulated, respectively. Gene ontology, pathway and network analyses showed that many of the mRNAs were involved in the regulation of classical pathways, including Notch signaling. Differential expression of a lncRNA signature composed of NONHSAT000264, FR075921, FR324124, linc-TRIM58, RP1-93H18.7, RP11-120 K9.2, RP11-134F2.2 and NONHSAG024980 was validated by quantitative reverse transcriptase-polymerase chain reaction analysis. **CONCLUSIONS:** This is the first report of differentially expressed lncRNAs in the P4-treated lung cancer cells. The results suggest that lncRNAs could serve as potential therapeutic targets for P4-sensitive lung cancer.

**IMPAD1 Functions as Mitochondrial Electron Transport Inhibitor That Prevents ROS Production and Promotes Lung Cancer Metastasis Through the AMPK-Notch1-HEY1 Pathway** Yi-Fang Yang 1 , Yen-Yun Wang 2 , Michael Hsiao 3 , et al. Steven Lo 4 , Yu-Chan Chang 5 , Yi-Hua Jan 5 , Tsung-Ching Lai 5 , Yi-Chen Lee 6 , Ya-Ching Hsieh 7, Cancer Lett. 2020 May 15;485:27-37. doi: 10.1016/j.canlet.2020.04.025. Online ahead of print.

The tumor microenvironment (TME) and metabolic reprogramming have been implicated in cancer development and progression. However, the link between TME, metabolism, and cancer progression in lung cancer is unclear. In the present study, we identified IMPAD1 from the conditioned medium of highly invasive CL1-5. High expression of IMPAD1 was associated with a poorer clinical phenotype in lung cancer patients, with reduced survival and increased lymph node metastasis. Knockdown of IMPAD1 significantly inhibited migration/invasion abilities and metastasis in vitro and in vivo. Upregulation of IMPAD1 and subsequent accumulation of AMP in cells increased the pAMPK, leading to Notch1 and HEY1 upregulation. As AMP is an ADORA1 agonist, treatment with ADORA1 inhibitor reduced the expression of pAMPK and HEY1 expression in IMPAD1-overexpressing cells. IMPAD1 caused mitochondria dysfunction by inhibiting mitochondrial Complex I activity, which reduced mitochondrial ROS levels and activated the AMPK-HEY1 pathway. Collectively this study supports the multipotent role of IMPAD1 in promotion of lung cancer metastasis by simultaneously increasing AMP levels, inhibition of Complex I activity to decrease ROS levels, thereby activating AMPK-Notch1-HEY1 signaling, and providing an alternative metabolic pathway in energy stress conditions.

[Prognostic Selection and Long-Term Survival Analysis to Assess Overdiagnosis Risk in Lung Cancer Screening Randomized Trials](#)

Eugenio Paci 1, Donella Puliti 2, Francesca Maria Carozzi 3, et al. *J Med Screen*. 2020 May 21;969141320923030. doi: 10.1177/0969141320923030.

**OBJECTIVES:** Overdiagnosis in low-dose computed tomography randomized screening trials varies from 0 to 67%. The National Lung Screening Trial (extended follow-up) and ITALUNG (Italian Lung Cancer Screening Trial) have reported cumulative incidence estimates at long-term follow-up showing low or no overdiagnosis. The Danish Lung Cancer Screening Trial attributed the high overdiagnosis estimate to a likely selection for risk of the active arm. Here, we applied a method already used in benefit and overdiagnosis assessments to compute the long-term survival rates in the ITALUNG arms in order to confirm incidence-excess method assessment. **METHODS:** Subjects in the active arm were invited for four screening rounds, while controls were in usual care. Follow-up was extended to 11.3 years. Kaplan-Meier 5- and 10-year survivals of "resected and early" (stage I or II and resected) and "unresected or late" (stage III or IV or not resected or unclassified) lung cancer cases were compared between arms.

**RESULTS:** The updated ITALUNG control arm cumulative incidence rate was lower than in the active arm, but this was not statistically significant (RR: 0.89; 95% CI: 0.67-1.18). A compensatory drop of late cases was observed after baseline screening. The proportion of "resected and early" cases was 38% and 19%, in the active and control arms, respectively. The 10-year survival rates were 64% and 60% in the active and control arms, respectively ( $p = 0.689$ ). The five-year survival rates for "unresected or late" cases were 10% and 7% in the active and control arms, respectively ( $p = 0.679$ ). **CONCLUSIONS:** This long-term survival analysis, by prognostic categories, concluded against the long-term risk of overdiagnosis and contributed to revealing how screening works.

[Liquid Biopsies Using Circulating Tumor DNA in Non-Small Cell Lung Cancer](#)

Bruna Pellini 1, Jeffrey Szymanski 2, Re-I Chin 2, Paul A Jones 2, Aadel A Chaudhuri 3 *Thorac Surg Clin*. 2020 May;30(2):165-177. doi: 10.1016/j.thorsurg.2020.01.005.

Liquid biopsies for the diagnosis and treatment of lung cancer have developed rapidly, driven primarily by technical advances in sensitivity to detect circulating tumor DNA (ctDNA). Still, technical limitations such as the challenge of detecting low-level ctDNA variants and distinguishing tumor-related variants from clonal hematopoiesis remain. With further technical advancements, new applications for ctDNA analysis are emerging including detection of post-treatment molecular residual disease (MRD), clinical trial selection, and early cancer detection. This chapter reviews the current state of ctDNA testing in NSCLC, the underlying technological advances enabling ctDNA detection, and the potential to expand ctDNA analysis to new applications.

[Screening Mammography Visits as Opportunities to Engage Smokers With Tobacco Cessation Services and Lung Cancer Screening](#)

Gary X Wang 1, Anand K Narayan 2, Elyse R Park 3, Constance D Lehman 2, Jonina T Gorenstein 4, Efren J Flores 2. *J Am Coll Radiol*. 2020 May;17(5):606-612. doi: 10.1016/j.jacr.2019.12.008. Epub 2020 Jan 10.

**OBJECTIVE:** Tobacco use is the leading cause of preventable mortality in the United States. Screening mammography (SM) visits present opportunities for radiology practices to reduce tobacco-related morbidity and mortality. Our study evaluates implementation of a program that provides tobacco cessation service referrals and screens for lung cancer screening (LCS) eligibility among smokers presenting for SM at a community health center. **METHODS:** In 2018, two sets of questions were added to our SM patient intake questionnaire to assess (1) smoking history and (2) interest in referral to the health center-based tobacco cessation program for mailed information, telephone-based consultation, and in-person counseling. Primary outcomes were proportion of current smokers who requested a referral and

of all smokers who were LCS-eligible. Bivariate logistic regression analyses compared sociodemographic characteristics of smokers who requested versus declined a referral. **RESULTS:** Of the 89.3% (1,907 of 2,136) who responded, 10.5% (201 of 1,907) were current and 29.1% (555 of 1,907) were former smokers. Of current smokers, 26.4% (53 of 201) requested referrals: mailed information by 23.9% (48 of 201), in-person counseling by 9% (18 of 201), and telephone-based consultation by 7.5% (15 of 201). No sociodemographic predictors for referral requests were identified. Of all smokers, 9.3% (70 of 756) were eligible for LCS, of which 31.4% (22 of 70) were up to date. **CONCLUSION:** One in ten women who underwent SM at our community health center were current smokers, of which one-quarter requested tobacco cessation referrals. Among LCS-eligible smokers, one-third were up to date. SM presents opportunities for radiology practices to advance population health goals such as tobacco cessation and LCS.

**[Collection and Handling of Thoracic Small Biopsy and Cytology Specimens for Ancillary Studies Guideline From the College of American Pathologists \(CAP\): Implications for the Cytology Community](#)** Paul A VanderLaan 1 J Am Soc Cytopathol. 2020 May 18;S2213-2945(20)30058-2. doi: 10.1016/j.jasc.2020.04.001. Online ahead of print.

The methods of collecting and handling thoracic small biopsy and cytology specimens can greatly impact downstream ancillary testing success, especially for non-small cell lung cancer (NSCLC). The College of American Pathologists (CAP) in collaboration with multiple other professional societies has recently developed an evidence-based laboratory practice guideline to provide clarity on how to best optimize these pre-analytic variables for small thoracic specimens. A total of 16 guideline statements were developed based on systematic literature review and expert panel consensus, covering topics ranging from optimal materials and techniques for fine-needle aspiration and small biopsy sampling to acquire sufficient amounts of material, to the use of rapid on-site evaluation to help appropriately triage, handle, and process these specimens. These guideline statements hold many implications for the practicing cytologist, though perhaps none more important than the recognition that the variety of cytology specimens we work with on a daily basis (including smears, cell blocks, and liquid-based cytology) can certainly be used for ancillary studies if supported by adequate validation studies. This commentary provides a brief overview of the newly developed CAP thoracic small biopsy and cytology specimen collection and handling guideline, as well as a discussion of how it may specifically impact the cytology community.

**[Molecular Testing on Bronchial Washings for the Diagnosis and Predictive Assessment of Lung Cancer](#)** Roberta Roncarati 1 2, Laura Lupini 1, Elena Miotto 1, et al. Mol Oncol. 2020 May 22. doi: 10.1002/1878-0261.12713. Online ahead of print.

Cyto-pathological analyses of bronchial washings (BWs) collected during fiberoptic bronchoscopy are often inconclusive for lung cancer diagnosis. To address this issue, we assessed the suitability of conducting molecular analyses on BWs, with the aim to improve the diagnosis and outcome prediction of lung cancer. The methylation status of RASSF1A, CDH1, DLC1, and PRPH was analysed in BW samples from 91 lung cancer patients and 31 controls, using a novel two-colour droplet digital methylation-specific PCR technique. Mutations in ALK, BRAF, EGFR, ERBB2, KRAS, MAP2K1, MET, NRAS, PIK3CA, ROS1, and TP53 and gene fusions of ALK, RET, and ROS1 were also investigated, using next-generation sequencing (NGS) on 73 lung cancer patients and 14 tumour-free individuals. Our four-gene methylation panel had significant diagnostic power, with 97% sensitivity and 74% specificity (relative risk, 7.3; odds ratio, 6.1; 95% confidence interval, 12.7-127). In contrast, gene mutation analysis had a remarkable value for predictive, but not for diagnostic, purposes. Actionable mutations in EGFR, HER2, and ROS1 as well as in other cancer genes (KRAS, PIK3CA, and TP53) were detected. Concordance with gene mutations uncovered in tumour biopsies was higher than 90%. In addition, bronchial-washing

analyses permitted complete patient coverage and the detection of additional actionable mutations. In conclusion, bronchial washings are a useful material on which to perform molecular tests based on gene panels: aberrant gene methylation and mutation analyses could be performed as approaches accompanying current diagnostic and predictive assays during the initial workup phase. This study establishes the grounds for further prospective investigation.

[A Rapid Liquid Biopsy of Lung Cancer by Separation and Detection of Exfoliated Tumor Cells From Bronchoalveolar Lavage Fluid With a Dual-Layer "PERFECT" Filter System](#) Tingyu Li 1, Yaoping Liu 1 2, Wei Zhang 3, et al. *Theranostics*. 2020 May 17;10(14):6517-6529. doi: 10.7150/thno.44274. eCollection 2020.

Separation and detection of exfoliated tumor cells (ETCs) from bronchoalveolar lavage fluid (BALF), namely the liquid biopsy of BALF, has been proved to be a valuable tool for the diagnosis of lung cancer. Herein, we established a rapid liquid biopsy of BALF based on a dual-layer PERFECT (precise, efficient, rapid, flexible, easy-to-operate, controllable and thin) filter system for the first time. **Methods:** The dual-layer PERFECT filter system consists of an upper-layer filter with large micropores (feature size of  $49.4 \pm 0.5 \mu\text{m}$ ) and a lower-layer filter with small micropores ( $9.1 \pm 0.1 \mu\text{m}$ ). The upper-layer filter contributes to the isolation of cell clusters and removal of mucus from BALF samples, meanwhile the lower-layer one targets for the separation of single ETCs. First, separation of 10000 spiked A549s (cultured lung cancer cells) from 10 mL clinical BALF samples (n=3) were performed to investigate the performance of the proposed system in rare cell separation. Furthermore, separation and detection of ETCs and ETC clusters from clinical BALF samples were performed with this system to test its efficacy and compared with the routine cytocentrifuge. The clinical BALF samples were collected from 33 lung cancer-suspected patients with visible lesions under bronchoscope. The final histopathological results showed that 20 samples were from lung cancer positive patients while the other 13 cases were from lung cancer negative patients. **Results:** The recovery rate of spiked A549 cells from clinical BALF samples with the developed system ( $89.8 \pm 5.2\%$ ) is significantly higher than that with the cytocentrifuge ( $13.6 \pm 7.8\%$ ). In the preliminary clinical trial, although 33 clinical BALF samples with volume ranging from 6 mL to 18 mL showed greatly varied turbidity, filtrations could be finished within 3 min for 54.6% of samples (18/33), and 10 min at most for the rest. The dual-layer PERFECT filter system is proved to have a much higher sensitivity (80.0%, 95% CI: 55.7%-93.4%) than the routine cytocentrifuge (45.0%, 95% CI: 23.8%-68.0%),  $p=0.016$  (McNemar test, two-tail). Moreover, the sensitivity of this platform is neither interfered by the variations of turbidity of the BALF samples, nor associated with the types of lung cancer. **Conclusions:** The easy and rapid processing of BALF samples with varying volume and turbidity, competitive sensitivity and good versatility for different lung cancer types will make the established dual-layer PERFECT filter system a promising approach for the liquid biopsy of BALF. The high-performance BALF-based liquid biopsy will improve the cytopathological identification and diagnosis of lung cancer.

[Results of Lung Cancer Screening in the Community](#) John R Handy Jr 1, Michael Skokan 2, Erika Rauch 3, Steven Zinck 4, Rachel E Sanborn 5, Svetlana Kotova 6, Mansen Wang 7 *Ann Fam Med*. 2020 May;18(3):243-249. doi: 10.1370/afm.2519.

**PURPOSE:** To address doubts regarding National Lung Screening Trial (NLST) generalizability, we analyzed over 6,000 lung cancer screenings (LCSs) within a community health system. **METHODS:** Our LCS program included 10 sites, 7 hospitals (2 non-university tertiary care, 5 community) and 3 free-standing imaging centers. Primary care clinicians referred patients. Standard criteria determined eligibility. Dedicated radiologists interpreted all LCSs, assigning Lung Imaging Reporting and Data System (Lung-RADS) categories. All category 4 Lung-RADS scans underwent multidisciplinary review and management recommendations. Data was prospectively collected from November 2013 through December 2018 and retrospectively analyzed. **RESULTS:** Of 4,666 referrals, 1,264 individuals were

excluded or declined, and 3,402 individuals underwent initial LCS. Second through eighth LCSs were performed on 2,758 patients, for a total of 6,161 LCSs. Intervention rate after LCS was 14.6% (500 individuals) and was most often additional imaging. Invasive interventions (n = 226) were performed, including 141 diagnostic procedures and 85 surgeries in 176 individuals (procedure rate 6.6%). Ninety-five lung cancers were diagnosed: 84 non-small cell (stage 1: 60; stage 2: 7; stage 3: 9; stage 4: 8), and 11 small cell lung cancers. The procedural adverse event rate was 23/226 (10.1%) in 21 patients (0.6% of all screened individuals). Pneumothorax (n = 10) was the most frequent, 6 requiring pleural drainage. There were 2 deaths among 85 surgeries or 2.3% surgical mortality. **CONCLUSIONS:** Our LCS experience in a community setting demonstrated lung cancer diagnosis, stage shift, intervention frequency, and adverse event rate similar to the NLST. This study confirms that LCS can be performed successfully, safely, and with equivalence to the NLST in a community health care setting.

**Relationships and Qualitative Evaluation Between Diffusion-Weighted Imaging and Pathologic Findings of Resected Lung Cancers** Katsuo Usuda 1, Shun Iwai 1, Aika Yamagata , et al. *Cancers* (Basel). 2020 May 8;12(5):E1194. doi: 10.3390/cancers12051194.

For detecting malignant tumors, diffusion-weighted magnetic resonance imaging (DWI) as well as fluoro-2-deoxy-glucose positron emission tomography/computed tomography (FDG-PET/CT) are available. It is not definitive how DWI correlates the pathological findings of lung cancer. The aim of this study is to evaluate the relationships between DWI findings and pathologic findings. In this study, 226 patients with resected lung cancers were enrolled. DWI was performed on each patient before surgery. There were 167 patients with adenocarcinoma, 44 patients with squamous cell carcinoma, and 15 patients with other cell types. Relationships between the apparent diffusion coefficient (ADC) of DWI and the pathology were analyzed. When the optimal cutoff value (OCV) of ADC for diagnosing malignancy was  $1.70 \times 10^{-3}$  mm<sup>2</sup>/s, the sensitivity of DWI was 92.0% (208/226). The sensitivity was 33.3% (3/9) in mucinous adenocarcinoma. The ADC value ( $1.31 \pm 0.32 \times 10^{-3}$  mm<sup>2</sup>/s) of adenocarcinoma was significantly higher than that ( $1.17 \pm 0.29 \times 10^{-3}$  mm<sup>2</sup>/s) of squamous cell carcinoma (p = 0.012), or ( $0.93 \pm 0.14 \times 10^{-3}$  mm<sup>2</sup>/s) of small cell carcinoma (p = 0.0095). The ADC value ( $1.91 \pm 0.36 \times 10^{-3}$  mm<sup>2</sup>/s) of mucinous adenocarcinoma was significantly higher than that ( $1.25 \pm 0.25 \times 10^{-3}$  mm<sup>2</sup>/s) of adenocarcinoma with mucin and that ( $1.24 \pm 0.30 \times 10^{-3}$  mm<sup>2</sup>/s) of other cell types. The ADC ( $1.11 \pm 0.26 \times 10^{-3}$  mm<sup>2</sup>/s) of lung cancer with necrosis was significantly lower than that ( $1.32 \pm 0.33 \times 10^{-3}$  mm<sup>2</sup>/s) of lung cancer without necrosis. The ADC of mucinous adenocarcinoma was significantly higher than those of adenocarcinoma of other cell types. The ADC of lung cancer was likely to decrease according to cell differentiation decreasing. The sensitivity of DWI for lung cancer was 92% and this result shows that DWI is valuable for the evaluation of lung cancer. Lung cancer could be evaluated qualitatively using DWI.

**Classifying Non-Small Cell Lung Cancer Types and Transcriptomic Subtypes Using Convolutional Neural Networks** Kun-Hsing Yu 1, Feiran Wang 2, Gerald J Berry 3, Christopher Ré 4, Russ B Altman 5 6 7, Michael Snyder 7, Isaac S Kohane 1 *J Am Med Inform Assoc*. 2020 May 1;27(5):757-769. doi: 10.1093/jamia/ocz230.

**OBJECTIVE:** Non-small cell lung cancer is a leading cause of cancer death worldwide, and histopathological evaluation plays the primary role in its diagnosis. However, the morphological patterns associated with the molecular subtypes have not been systematically studied. To bridge this gap, we developed a quantitative histopathology analytic framework to identify the types and gene expression subtypes of non-small cell lung cancer objectively. **MATERIALS AND METHODS:** We processed whole-slide histopathology images of lung adenocarcinoma (n = 427) and lung squamous cell carcinoma patients (n = 457) in the Cancer Genome Atlas. We built convolutional neural networks to classify

histopathology images, evaluated their performance by the areas under the receiver-operating characteristic curves (AUCs), and validated the results in an independent cohort (n = 125).

**RESULTS:** To establish neural networks for quantitative image analyses, we first built convolutional neural network models to identify tumor regions from adjacent dense benign tissues (AUCs > 0.935) and recapitulated expert pathologists' diagnosis (AUCs > 0.877), with the results validated in an independent cohort (AUCs = 0.726-0.864). We further demonstrated that quantitative histopathology morphology features identified the major transcriptomic subtypes of both adenocarcinoma and squamous cell carcinoma (P < .01). **DISCUSSION:** Our study is the first to classify the transcriptomic subtypes of non-small cell lung cancer using fully automated machine learning methods. Our approach does not rely on prior pathology knowledge and can discover novel clinically relevant histopathology patterns objectively. The developed procedure is generalizable to other tumor types or diseases.

### [Safe Performance of Diagnostic bronchoscopy/EBUS During the SARS-CoV-2 Pandemic](#)

Daniel P Steinfert 1 2, Felix J F Herth 3 4, Louis B Irving 1, Phan T Nguyen 5 *Respirology*. 2020 May 13;10.1111/resp.13843. doi: 10.1111/resp.13843. Online ahead of print.

The SARS-CoV-2 pandemic is unprecedented in our professional lives and much effort and resources will be devoted to care of patients (and HCW) affected by this illness. We must also continue to aim for the same standard of care for our non-COVID respiratory patients, while minimizing risks of infection transmission to our colleagues. This commentary addresses the key paired issues of minimizing performance of diagnostic/staging bronchoscopy in patients with suspected/known lung cancer while maximizing the safety of the procedure with respect to HCW transmission of COVID-19.

### [Exploring the Impact of Lung Cancer Screening on Lung Cancer Mortality of Smokers With Obstructive Lung Disease: Analysis of the NLST-ACRIN Cohort](#)

Juan P de-Torres 1, Juan P Wisnivesky 2, Gorka Bastarrika 3, David O Wilson 4, Bartolome R Celli 5, Javier J Zulueta 6 *Arch Bronconeumol*. 2020 May 12;S0300-2896(20)30104-6. doi: 10.1016/j.arbres.2020.03.023. Online ahead of print.

**BACKGROUND:** Lung Cancer (LC) screening with low dose chest computed tomography (LDCT) in smokers reduces LC mortality. Patients with Obstructive Lung Disease (OLD) are at high risk for LC. The potential effect of LC screening in this population is unknown. **OBJECTIVE:** To determine if screening with LDCT reduces LC mortality in smokers with spirometrically defined OLD. **METHODS:** The National Lung Screening Trial-American College of Radiology Imaging Network (NLST-ACRIN) study included 13,831 subjects (55-74 years of age with  $\geq 30$  pack-year history of smoking) that had a baseline spirometry. Randomly assigned to LDCT or Chest X-ray, all had 3 annual rounds of screening. LC mortality was compared between the LDCT and chest X-ray arms during the 1st year and at 6 years of follow up. Landmark analysis explored LC mortality differences between arms after the first year.

**RESULTS:** From the 4584 subjects with OLD (FEV1/FVC <0.7), 152 (3.3%) died from LC. Multivariable analysis showed that screening trended to decrease LC mortality at 6 years (HR, 95%CI: 0.75, 0.55-1.04, p=0.09). During the 1st year no differences were found between arms (p=0.65). However, after this year, LDCT significantly decreased LC mortality (HR, 95%CI: 0.63, 0.44-0.91, p=0.01). The number needed to screen to avoid one LC death in these subjects was 108 while in those without OLD was 218. **CONCLUSIONS:** LC screening with LDCT in smokers with spirometrically diagnosed OLD, showed a trend to reduce lung cancer mortality but a study with a larger number of patients and with a more robust design would be needed to confirm these findings.

### Education Level Predicts Appropriate Follow-Up of Incidental Findings From Lung Cancer

**Screening** Suraj Kapoor 1, Stephen A Deppen 2, Alexis B Paulson 3, Diane Haddad 4, James P Cook 3, Kim L Sandler 3. J Am Coll Radiol. 2020 May;17(5):613-619. doi: 10.1016/j.jacr.2019.12.014. Epub 2020 Jan 10.

**PURPOSE:** The aim of this study was to identify predictors of appropriate follow-up for clinically significant incidental findings (IFs) detected with low-dose CT during lung cancer screening.

**METHODS:** Charts of 1,458 prospectively enrolled lung screening patients from January 1, 2015, to October 31, 2018, were reviewed. IFs, other than coronary artery calcification and emphysema, were identified. ACR practice guidelines defined appropriate patient follow-up. Patient demographic and social characteristics were obtained from the initial shared decision-making visit and the electronic medical record. Factors of interest included age, gender, race, education level, and insurance status. Education level was reported as high school graduate or less or education past high school. A multivariate logistic regression was estimated to assess patient factors associated with appropriate follow-up. **RESULTS:** One hundred thirty-eight participants (9%) with 141 actionable IFs were identified. The overall appropriate follow-up rate was 82%. The most common IFs were renal lesions (16%), dilated thoracic aorta (10%), and pulmonary fibrosis (10%). Univariate analysis of appropriate patient follow-up revealed a significant difference for education level ( $P = .02$ ). A greater than high school education remained strongly associated with appropriate follow-up after controlling for other demographic factors. **CONCLUSIONS:** Appropriate patient follow-up of clinically significant IFs from lung cancer screening is a well-recognized avenue to improve population health. Education level is a significant independent predictor of appropriate follow-up of IFs, whether as a surrogate for low socioeconomic status or as an indication of health literacy. To address these realities, lung screening shared decision making should adapt to consider health care access and health literacy.

### Values of Different Specimen Preparation Methods for the Diagnosis of Lung Cancer by Endobronchial Ultrasound Guided Transbronchial Needle Aspiration

Youzu Xu 1, Jian Lin 1, Meifang Chen 2, Haihong Zheng 3, Jiayi Feng 1 et al. BMC Pulm Med. 2020 May 15;20(1):140. doi: 10.1186/s12890-020-01183-x.

**BACKGROUND:** Endobronchial ultrasound guided transbronchial needle aspiration (EBUS-TBNA) has become an important procedure for the diagnosis and staging of lung cancer. Our research identified the effects of different pathological preparation on the diagnosis of lung cancer for specimens obtained by biopsy. **METHODS:** Patients were clinically considered if lung cancer was accompanied by mediastinal or hilar lymph node enlargement between March 2014 and November 2017. Specimens obtained by EBUS-TBNA were treated by three methods: traditional smear cytology, liquid-based cytology (LBC) and histopathology. **RESULTS:** Of a total of 154 puncture sites from 153 patients, the total positive rate of combination for the three pathological treatment types (histopathology, direct traditional smear, and LBC) was 77.3%. The diagnostic positive rate for histopathology was 68.6%, direct traditional smear was 65.6%, and LBC was 60.4%; there was no significant differences among the three single pathological treatment types ( $P = 0.29$ ), but there was a statistically significant difference between the combination of three treatments and any single pathological treatment type ( $P = 0.01$ ). The diagnostic sensitivities of histopathology combined with traditional smear and histopathology combined LBC were 94.4 and 92.8%, respectively, the specificities and PPVs were both 100%, and the diagnostic accuracies were 95.5 and 94.2%, respectively; the sensitivities, specificities and diagnostic accuracies above were all higher than those of single specimen treatment and lower than those of the three combined. **CONCLUSION:** When EBUS-TBNA is used for the diagnosis and staging of lung cancer, the use of histopathological sections combined with direct cytological smear should be sufficient and is the most economical choice.



## NSCLC - SURGERY

[The Association of Nodal Upstaging With Surgical Approach and Its Impact on Long-Term Survival After Resection of Non-Small-Cell Lung Cancer](#)

Mark W Hennon<sup>1 2</sup>, Luke H DeGraaff<sup>2</sup>, Adri Eur J Cardiothorac Surg. 2020 May 1;57(5):888-895. doi: 10.1093/ejcts/ezz320.enne Groman<sup>3</sup>, Todd L Demmy<sup>1 2</sup>, Sai Yendamuri<sup>1 2</sup>

**OBJECTIVES:** Proponents of open thoracotomy (OPEN) and robot-assisted thoracic surgery (RATS) claim its oncological superiority over video-assisted thoracic surgery (VATS) in terms of the accuracy of lymph node staging. **METHODS:** The National Cancer Database was queried for patients with non-small-cell lung cancer (NSCLC) undergoing lobectomy without neoadjuvant therapy from 2010 to 2014. Nodal upstaging rates were compared using a surgical approach. Overall survival adjusted for confounding variables was examined using the Cox proportional hazards model. **RESULTS:** A total of 64 676 patients fulfilled the selection criteria. The number of patients who underwent lobectomy by RATS, VATS and OPEN approaches was 5470 (8.5%), 17 545 (27.1%) and 41 661 (64.4%), respectively. The mean number of lymph nodes examined for each of these approaches was 10.9, 11.3 and 10 (P < 0.01) and upstaging rates were 11.2%, 11.7% and 12.6% (P < 0.01), respectively. For patients with clinical stage I disease (N = 46 826; RATS = 4338, VATS = 13 416 and OPEN = 29 072), the mean lymph nodes examined were 10.6, 10.8 and 9.4 (P < 0.01), and upstaging rates were 10.8%, 11.1% and 12.1% (P < 0.01), respectively. A multivariable analysis suggested an association with improved survival with RATS and VATS compared with OPEN surgery [hazard ratio (HR) = 0.89 and 0.89, respectively; P < 0.01] for patients with all stages. In stage I disease, VATS but not RATS was associated with increased overall survival compared with the OPEN approach (HR = 0.81; P < 0.01). **CONCLUSIONS:** RATS lobectomy is not superior to VATS lobectomy with respect to lymph node yield or upstaging of NSCLC. Increased nodal upstaging by the OPEN approach does not confer a survival advantage in any stage of NSCLC and may be associated with decreased overall survival.

[Complex Sleeve Lobectomy Has the Same Surgical Outcome When Compared With Conventional Lobectomy in Patients With Lung Cancer](#)

Ilhan Inci<sup>1</sup>, Martina Benker<sup>1</sup>, Necati Çitak<sup>1 2</sup>, Didier Schneider<sup>1</sup>, Claudio Caviezel<sup>1</sup>, Sven Hillinger<sup>1</sup>, Isabelle Opitz<sup>1</sup>, Walter Weder<sup>1</sup> Eur J Cardiothorac Surg. 2020 May 1;57(5):860-866. doi: 10.1093/ejcts/ezz357.

**OBJECTIVES:** No significant data are available to assess whether complex sleeve lobectomy (complex-SL) can be considered comparable to conventional lobectomy (CL) in terms of surgical outcome. The purpose of this study was to compare surgical and oncological outcomes of complex-SL with CL in patients with lung cancer. **METHODS:** Between 2000 and 2015, a total of 568 patients who underwent open CL (defined as resection of only 1 lobe) and 187 patients who underwent SL were analysed. The SL group was divided into 2 subgroups: standard-SL (bronchial SL, n = 106) and complex-SL (n = 81) (defined as bronchial sleeve resection together with another surgical intervention: bronchovascular SL, n = 40; vascular SL, n = 26; atypical bronchoplasty with resection of more than 1 lobe, n = 12; bronchial SL + chest wall resection, n = 3). **RESULTS:** The complex-SL group had more patients with chronic obstructive pulmonary disease (COPD) (25.9% vs 12.5%, P = 0.001), neoadjuvant treatment (39.5% vs 12.0%, P < 0.001), advanced-stage non-small-cell lung cancer (53.2% vs 33.1%, P = 0.001) and low preoperative forced expiratory volume in 1 s (77.2% vs 84.3%, P = 0.004) than the CL group. The overall surgical mortality (in-hospital or 30-day) was 2.6% (n = 20); it was 2.8% for CL and 2.8% for complex-SL. Postoperative complications occurred in 34.9% of the CL group and 39.5% of the complex-SL group (P = 0.413). The pulmonary complication rate was similar between the groups (24.1% for CL, 27.2% for complex-SL, P = 0.552). The 5-year survival in the CL group was 57.1%, and in the complex-SL group it

was 56.2% (P = 0.888). Multivariate analysis showed that TNM stage (P < 0.001) and N status (P < 0.001) were significant and independent negative prognostic factors for survival. **CONCLUSIONS:** Complex-SL had a comparable outcome to CL, although the complex-SL group had more patients with advanced-stage NSCLC, low preoperative forced expiratory volume in 1 s and COPD.

**Outcomes of Lobectomy on Pulmonary Function for Early Stage Non-Small Cell Lung Cancer (NSCLC) Patients With Chronic Obstructive Pulmonary Disease (COPD)** Sen Wei<sup>1</sup>, Feng Chen<sup>1</sup>,

Renwang Liu<sup>1 2</sup>, et al. *Thorac Cancer*. 2020 May 6. doi: 10.1111/1759-7714.13445. Online ahead of print.

**BACKGROUND:** Lung cancer is the first cause of cancer mortality worldwide. Chronic obstructive pulmonary disease (COPD) is an independent risk factor for lung cancer. An epidemiological survey discovered that the presence of COPD increases the risk of lung cancer by 4.5-fold. Lobectomy is considered to be the standard surgical method for early stage non-small cell lung cancer (NSCLC). However, the influence of lobectomy on the loss of pulmonary function has not been fully investigated in NSCLC patients with COPD. **METHODS:** We searched the PubMed database using the following strategies: COPD and pulmonary function test (MeSH term) and lobectomy (MeSH term) from 01 January 1990 to 01 January 2019. We selected the articles of patients with COPD. A total of six studies, including 195 patients with COPD, provided lung function values before and after surgery.

**RESULTS:** Five out of six studies focused on the short-term change of pulmonary function (within 3-6 months) after lobectomy, and the average loss of FEV1 was 0.11 L (range: -0.33-0.09 L). One study investigated the long-term change of pulmonary function (within 1-2 years) after lobectomy, and the average loss of FEV1 was 0.15 L (range: -0.29-0.05 L). **CONCLUSIONS:** A short-term (3-6 months) loss of pulmonary function after operation is acceptable for lung cancer patients with COPD. However, there may be a high risk of postoperative complications in NSCLC patients with COPD. Therefore, surgical treatment needs to be carefully considered for these patients.

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**NSCLC – SYSTEMIC THERAPIES (CHEMOTHERAPY, TARGETED THERAPY, AND IMMUNOTHERAPY)**

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**Treatment- And Immune-Related Adverse Events of Immune Checkpoint Inhibitors in Advanced Lung Cancer** Jun Shao<sup>1</sup>, Chengdi Wang<sup>1</sup>, Pengwei Ren<sup>2</sup>, Yuting Jiang<sup>3</sup> Panwen Tian<sup>1</sup>, Weimin Li<sup>1</sup>

*Biosci Rep*. 2020 May 29;40(5):BSR20192347. doi: 10.1042/BSR20192347.

**BACKGROUND:** Immune checkpoint inhibitors (ICIs) emerged as the preferred therapy in advanced lung cancer, understanding the treatment- and immune-related adverse events of these drugs is of great significance for clinical practice. **MATERIALS AND METHODS:** PubMed, Embase, Cochrane library and major conference proceedings were systematically searched for all randomized controlled trials (RCTs) in lung cancer using PD-1/PD-L1/CTLA-4 inhibitors. The outcomes included treatment-related adverse events (TRAEs) and several organ specific immune-related adverse events (IRAEs).

**RESULTS:** 24 RCTs involving 14,256 patients were included. There was a significant difference for ICI therapy in the incidence of any grade of TRAEs (RR: 0.90; 95%CI: 0.84-0.95; P=0.001) and a lower frequency of grade 3-5 of TRAEs (RR: 0.65; 95%CI: 0.51-0.82; P<0.001). Patients treated with ICI therapy in non-small-cell lung cancer (NSCLC) were less reported TRAEs than in small cell lung cancer (SCLC). A lower risk of TRAEs was favored by anti-PD-1 inhibitors over anti-PD-L1 antibodies and anti-CTLA-4 drugs. The most common organ specific IRAE was hypothyroidism that occurred 8.7%. The incidence of pneumonitis and hepatitis reached 4.5% and 4.0% respectively. Compared with patients treated in control arms, those treated with ICI drugs were at higher risk for each organ specific adverse event including colitis, hepatitis, pneumonitis, hypothyroidism and hypophysitis. **CONCLUSIONS:** ICI therapy was safer than chemotherapy, especially ICI monotherapy such as anti-PD-1 antibodies in

NSCLC. Compared with standard treatments, ICI drugs increased the risk of organ-specific IRAEs, although the overall incidence remained low.

**[Duration of Nivolumab for Pretreated, Advanced Non-Small-Cell Lung Cancer](#)** Margaux Geier<sup>1</sup>, Renaud Descourt<sup>1</sup>, Romain Corre<sup>2</sup>, et al. *Cancer Med.* 2020 May 15. doi: 10.1002/cam4.3120. Online ahead of print.

**BACKGROUND:** A standard of care for pretreated, advanced non-small-cell lung cancers (NSCLCs), nivolumab has demonstrated long-term benefit when administered for 2 years. We aimed to better discern an optimized administration duration by retrospectively analyzing real-life long-term efficacy in a prospective cohort. **METHODS:** All nivolumab-treated adults with advanced NSCLCs (01/09/2015 to 30/09/2016) from nine French centers were eligible. On 31/12/2018, patients who are alive  $\geq 2$  years after starting nivolumab were defined as long-term survivors (LTSs) and were divided into three nivolumab treatment groups:  $< 2$ , 2, or  $> 2$  years. Co-primary endpoints were LTSs' progression-free survival (PFS) and overall survival (OS). **RESULTS:** The median follow-up was 32 months (95% CI, 31.0 to 34.0). The 3-year OS rate for the 259 cohort patients was 16.6%. Among them, 65 were LTSs: 47 treated  $< 2$  years, 7 for 2 years, and 11  $> 2$  years. Their respective characteristics were: median age: 59, 52, and 58 years; smoking history: 92.9, 100, and 100%; adenocarcinomas: 66, 57.1, and 54.5%. LTSs' median (m)PFS was 28.4 months; mOS was not reached. LTSs' objective response rate was 61.6%. mOS was 32.7 months for those treated  $< 2$  years and not reached for the others. The  $> 2$ -year group's 3-year OS was longer. Twenty-eight LTSs experienced no disease progression; 7 had durable complete responses. However, LTSs had more frequent and more severe adverse events. **CONCLUSION:** In real-life, prolonged nivolumab use provided long-term benefit with 16.6% 3-year OS and 25% LTSs. Survival tended to be prolonged with nivolumab continued beyond 2 years. Prospective randomized trials with adequate design are needed.

**[PIOS \(Patras Immunotherapy Score\) Score Is Associated With Best Overall Response, Progression-Free Survival, and Post-Immunotherapy Overall Survival in Patients With Advanced Non-Small-Cell Lung Cancer \(NSCLC\) Treated With Anti-Program Cell Death-1 \(PD-1\) Inhibitors](#)**

*Cancers (Basel)*. 2020 May 16;12(5):E1257. doi: 10.3390/cancers12051257.

Foteinos-Ioannis Dimitrakopoulos<sup>1 2</sup>, Achilleas Nikolakopoulos<sup>1</sup>, Anastasia Kottorou, et al. *Cancers (Basel)*. 2020 May 16;12(5):E1257. doi: 10.3390/cancers12051257.

Immunotherapy with immune checkpoint inhibitors (ICIs) has changed the therapeutic management of advanced non-small cell lung cancer (aNSCLC) over the last decade. However, there is an unmet need for clinically useful biomarkers in this patient subgroup. The aim of this study was to combine baseline clinical characteristics of aNSCLC patients, in the form of a scoring system, and to investigate its predictive and prognostic value in NSCLC patients treated with ICIs. A total of 112 patients with advanced (stages IIIA to IV) NSCLC, treated with nivolumab or pembrolizumab, were enrolled in this study. Patras Immunotherapy Score (PIOS) was developed based on four of the studied parameters (performance status (PS), body mass index (BMI), age, and lines of treatment (LOT), which were incorporated into our formula ( $PS \times BMI / LOT \times age$ ). PIOS score was strongly associated with best overall responses (BOR), with those patients having benefit/good response (stable disease (SD) or partial (PR) or complete response (CR), achieving a higher score compared to patients who developed progressive disease (PD) ( $p < 0.001$ ). Furthermore, PIOS score was associated with progression-free survival (PFS), since high-score patients had longer PFS ( $p < 0.001$ , hazard ratio (HR) = 0.469). Moreover, PIOS was associated with post-immunotherapy overall survival (OS), with high-score patients having improved OS (log-rank  $p = 0.019$ ). This study suggests that a combination of baseline parameters, which give rise to PIOS score, may predict the best response of NSCLC patients treated with anti-

program cell death -1 (PD-1) monotherapy as well as it may have a potent prognostic value for PFS and post immunotherapy OS.

### **Serum Markers Associated With Treatment Response and Survival in Non-Small Cell Lung Cancer Patients Treated With anti-PD-1 Therapy**

Kazuki Takada 1, Shinkichi Takamori 2, Yasuto Yoneshima 3, et al. Lung Cancer. 2020 Jul;145:18-26. doi: 10.1016/j.lungcan.2020.04.034. Epub 2020 May 5.

**BACKGROUND:** Several serum markers have been associated with treatment response and clinical outcome in non-small cell lung cancer (NSCLC) patients treated with immune checkpoint inhibitors.

**MATERIALS AND METHODS:** We performed univariate and multivariate analyses on 226 patients with advanced or recurrent NSCLC treated with anti-programmed cell death-1 (PD-1) therapy. The cut-off values for body mass index (BMI), albumin (Alb), and serum inflammatory markers were determined by receiver operating characteristic curve analyses. Tumor response was assessed by computed tomography according to the Response Evaluation Criteria in Solid Tumors, version 1.1. **RESULTS:**

BMI  $\geq$  19.1 kg/m<sup>2</sup> and derived neutrophil-lymphocyte ratio (dNLR)  $<$  2.79 were independent predictors of overall response, and Alb  $\geq$  3.5 g/dL and dNLR  $<$  2.79 were independent predictors of disease control. Analyses of survival revealed that Alb  $<$  3.5 g/dL, dNLR  $\geq$  2.79, lymphocyte-monocyte ratio  $<$  2.12, and red blood cell distribution width  $\geq$  15.9 % were independent predictors of both progression-free and overall survival. Moreover, these markers tended to have a strong impact on survival, especially among patients with programmed cell death-ligand 1 tumor proportion score  $\geq$  50 %. **CONCLUSIONS:** dNLR might be the most important factor for predicting the efficacy in NSCLC patients treated with anti-PD-1 therapy.

### **Efficacy of Immunotherapy Targeting the Neoantigen Derived From EGFR T790M/C797S**

**Mutation in Non-Small Cell Lung Cancer** Yu Akazawa 1 2 , Yuki Saito 1 , Toshiaki Yoshikawa 1 , et al. Cancer Sci. 2020 May 11. doi: 10.1111/cas.14451. Online ahead of print.

Lung cancer is the leading cause of cancer-related deaths worldwide. Epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) have often good clinical activity against non-small cell lung cancer (NSCLC) with activating EGFR mutations. Osimertinib, which is third-generation EGFR-TKI, provides clinical effect even on NSCLC harboring the threonine to methionine change at codon 790 of EGFR (EGFR T790M) mutation that cause TKI resistance. However, most NSCLC patients develop acquired resistance to Osimertinib within about one year, and 40% of these patients have the EGFR T790M and cysteine to serine change at codon 797 (C797S) mutations. Therefore, there is an urgent need for the development of novel treatment strategies for NSCLC patients with the EGFR T790M/C797S mutation. In this study, we novelty identified the EGFR T790M/C797S mutation-derived peptide (790-799) (MQLMPFGSLL) that binds the human leukocyte antigen (HLA)-A\*02:01, and successfully established EGFR T790M/C797S-peptide-specific cytotoxic T lymphocyte (CTL) clones from human peripheral blood mononuclear cells (PBMCs) of HLA-A2 healthy donors. One established CTL clone demonstrated adequate cytotoxicity against T2 cells pulsed with the EGFR T790M/C797S peptide. This CTL clone also had high reactivity against cancer cells that expressed an endogenously EGFR T790M/C797S peptide using an interferon- $\gamma$  (IFN- $\gamma$ ) enzyme-linked immunospot (ELISPOT) assay. In addition, we demonstrated using a mouse model that EGFR T790M/C797S peptide-specific CTLs were induced by EGFR T790M/C797S peptide vaccine in vivo. These findings suggest that an immunotherapy targeting a neoantigen derived from EGFR T790M/C797S mutation could be a useful novel therapeutic strategy for NSCLC patients with EGFR-TKI resistance, especially resistant to Osimertinib.

### **Predictive and Prognostic Impact of Primary Tumor-Bearing Lobe in Nonsmall Cell Lung Cancer Patients Treated With anti-PD-1 Therapy**

Shinkichi Takamori 1 , Kazuki Takada 2 , et al. Int J Cancer. 2020 May 1. doi: 10.1002/ijc.33030. Online ahead of print.

Immunotherapy targeting programmed cell death-1 (PD-1) has become a standard pharmacological therapy. Although tumor mutation burden level was reported to depend on the tumor location in nonsmall cell lung cancer (NSCLC), predictive impact of the tumor location on the response to anti-PD-1 therapy is unknown. Two hundred and seventeen advanced or recurrent NSCLC patients treated with anti-PD-1 therapy at Kyushu University Hospital and National Hospital Organization Kyushu Cancer Center were analyzed. To minimize the bias arising from the patients' background, adjusted Kaplan-Meier survival curves and Cox proportional hazards regression analyses using inverse probability of treatment weights (IPTW) were performed. Of the 217 patients, 132, 27, and 58 had primary NSCLC in upper, middle, and lower lobes, respectively. Patients with NSCLC in upper lobe were significantly associated with younger age ( $P = .0070$ ) and smoker ( $P = .0003$ ). The epidermal growth factor receptor-wild type and tumor location in upper lobe were independent predictors of disease control ( $P = .0175$  and  $P = .0425$ , respectively). The IPTW-adjusted Kaplan-Meier curves showed that patients with NSCLC in the upper lobes had significantly longer progression-free survival (PFS) and overall survival (OS) than those in middle/lower lobes ( $P = .0026$  and  $P = .0015$ , respectively). On IPTW adjusted Cox analysis, NSCLC in the upper lobe was an independent predictor of PFS and OS ( $P = .0078$  and  $P = .0034$ , respectively). Patients with primary NSCLC in the upper lobes may be good candidates for anti-PD-1 therapy. These findings should be validated prospectively.

**[Adjuvant and Neoadjuvant Immunotherapy in Non-small Cell Lung Cancer](#)** Stephen R Broderick 1  
Thorac Surg Clin. 2020 May;30(2):215-220. doi: 10.1016/j.thorsurg.2020.01.001.

The advent of immune checkpoint blockade has revolutionized the management of advanced non-small cell lung cancer (NSCLC). Impressive results in the metastatic setting have prompted substantial interest in the application of these agents in earlier-stage disease. Applications of checkpoint blockade in the adjuvant setting are under investigation in several clinical trials. Early trials have demonstrated the safety and feasibility of the administration of checkpoint inhibitors in the neoadjuvant setting. Resection specimens demonstrate encouraging rates of pathologic response. There are several ongoing phase 3 studies comparing neoadjuvant combination chemotherapy and checkpoint blockade to chemotherapy alone in patients with resectable NSCLC.

**[Principles of Immunotherapy in Non-Small Cell Lung Cancer](#)** Melinda L Hsu 1 , Jarushka Naidoo 2  
Thorac Surg Clin. 2020 May;30(2):187-198. doi: 10.1016/j.thorsurg.2020.01.009.

Immunotherapy has transformed the treatment of many tumors. Robust data demonstrating improved overall survival and progression-free survival in patients treated with monoclonal antibodies have established immune checkpoint inhibitors as standard of care in stages III and IV non-small cell lung cancer. Nivolumab is effective in previously treated patients with metastatic non-small cell lung cancer. Pembrolizumab and atezolizumab are approved as monotherapy and in combination with other therapies. Ongoing trials investigate the potential role of immunotherapy in earlier disease settings. Identifying predictive biomarkers of response will further amplify the impact of immune checkpoint inhibitors in the treatment of non-small cell lung cancer.

**[Immune Checkpoint Inhibitors for Lung Cancer Treatment: A Review](#)** Keisuke Onoi 1, Yusuke Chihara 1, Junji Uchino 1, et al. J Clin Med. 2020 May 6;9(5):E1362. doi: 10.3390/jcm9051362.

The treatment of lung cancer has changed drastically in recent years owing to the advent of immune checkpoint inhibitors (ICIs). A 1992 study reported that programmed cell death-1 (PD-1), an immune checkpoint molecule, is upregulated during the induction of T cell death. Since then, various immunoregulatory mechanisms involving PD-1 have been clarified, and the successful use of PD-1 blockers in anticancer therapy eventually led to the development of the current generation of ICIs. Nivolumab was the first ICI approved for treating lung cancer in 2014. Since then, various ICIs such as

pembrolizumab, atezolizumab, and durvalumab have been successively introduced into clinical medicine and have shown remarkable efficacy. The introduction of ICIs constituted a major advancement in lung cancer treatment, but disease prognosis continues to remain low. Therefore, new molecular-targeted therapies coupled with existing anticancer drugs and radiotherapy have recently been explored. This review encompasses the current status, challenges, and future perspectives of ICI treatment in lung cancer.

**[PD-L1 Expression and Response to Pembrolizumab in Patients With EGFR-mutant Non-Small Cell Lung Cancer](#)** Eriko Miyawaki 1, Haruyasu Murakami 1 Keita Mori 2 , et al. Jpn J Clin Oncol. 2020 May 5;50(5):617-622. doi: 10.1093/jjco/hyaa033.

Epidermal growth factor receptor (EGFR)-mutant non-small cell lung cancer is less likely to express programmed death-ligand 1 (PD-L1) than tumors with wild-type EGFR and is associated with poor response to pembrolizumab. To understand the relationship between EGFR mutation and PD-L1 expression in pembrolizumab response, we retrospectively evaluated the factors contributing to the high tumor proportion score in 155 EGFR-mutant non-small cell lung cancer cases and their associated response to pembrolizumab. Uncommon EGFR mutations were significantly associated with a PD-L1 tumor proportion score  $\geq 50\%$  compared to common EGFR mutations. The objective response rate to pembrolizumab of 14 patients was 36%, including 22% in patients with common EGFR mutations, 60% in patients with uncommon EGFR mutations and 75% in patients with both uncommon mutations and a PD-L1 tumor proportion score  $\geq 50\%$ . A PD-L1 tumor proportion score  $\geq 50\%$  was more frequent in non-small cell lung cancer patients harboring uncommon EGFR mutations and was associated with pembrolizumab efficacy.

**[Acquired Resistance to Osimertinib in Patients With Non-Small-Cell Lung Cancer: Mechanisms and Clinical Outcomes](#)** Yuxin Mu 1, Xuezhi Hao 1, Puyuan Xing 1, et al. J Cancer Res Clin Oncol. 2020 May 8. doi: 10.1007/s00432-020-03239-1. Online ahead of print.

**PURPOSE:** Osimertinib, a third-generation epidermal growth factor receptor tyrosine-kinase inhibitor (EGFR-TKI), has demonstrated substantial clinical benefit in patients with non-small-cell lung cancer (NSCLC) who were resistant to early-generation EGFR-TKIs and had acquired a T790M mutation. The aim of our study was to identify the mechanisms underlying resistance to osimertinib and to correlate them with clinical outcomes. **METHODS:** We retrospectively analyzed patients with advanced NSCLC who received osimertinib for T790M-mutated acquired resistance to prior EGFR-TKIs between March 1, 2017 and December 31, 2018. Patients with paired molecular data of pre-osimertinib and after resistance development, which were not confirmed with small-cell lung cancer (SCLC) transformation, were included in the molecular analysis set. **RESULTS:** Of 49 patients evaluated in the molecular analysis set, 24 patients maintained T790M mutation, while 25 patients exhibited T790M-loss. Molecular modifications were identified in 27 of 49 patients including EGFR acquired mutations (C797S, C796S, G796S, V802I, V834L, E758D and G724S), non-EGFR-dependent mutations (PIK3CA, ALK, BRAF, KRAS and TP53), EGFR amplification and MET amplification. At data cutoff, median progression-free survival (PFS) was 9.3 months in the T790M-retain group compared with 7.8 months in T790M-loss patients ( $P = 0.053$ ). Median PFS was significantly longer in patients with EGFR-dependent resistance mechanism (13.5 months) than in those with alternative pathway activation (8.2 months;  $P = 0.012$ ). **CONCLUSIONS:** The study revealed heterogeneous mechanisms of resistance to osimertinib in advanced NSCLC patients and their association with clinical outcomes. Patients who maintained T790M mutation or with EGFR-dependent resistance mechanism had longer clinical outcome benefits

[Systemic Treatment of Brain Metastases in Non-Small Cell Lung Cancer](#) Simon Page 1, Charlotte Milner-Watts 1, Marco Perna 2, et al. Eur J Cancer. 2020 Jun;132:187-198. doi: 10.1016/j.ejca.2020.03.006. Epub 2020 May 4.

Brain metastases (BrMs) are associated with significant morbidity and are found in up to 50% of patients with advanced non-small cell lung cancer (NSCLC). Most of the literature focuses on symptomatic BrMs, with a lack of baseline brain imaging in asymptomatic patients. Unfortunately, much of the data on local treatments with or without systemic treatment is retrospective. Clinical trials of systemic treatments largely exclude patients with BrMs. Chemotherapy is an active treatment for BrM with response rates in the brain similar to other sites of disease. Targeted systemic treatments in patients with driver mutations (EGFR and ALK-MET to date) 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, but retrospective data suggest that early local therapies may give better intracranial progression-free survival (ICPFS). Recent immunotherapy trials have included patients with BrMs. These patients have largely been pre-treated with local therapies and are asymptomatic. Thus, the current standard is becoming, early local therapies before or in conjunction with immunotherapy agents. The approach seems to be safe. Prospective studies are needed in NSCLC BrMs patients to make sure any benefit from local therapies on the ICPFS and quality of life is not overlooked. Here we report what we think are reasonable conclusions from the available data and make suggestions for future clinical trials in the management of NSCLC BrMs.

[Programmed Death Ligand 1 Heterogeneity and Its Impact on Benefit From Immune Checkpoint Inhibitors in Non-Small-Cell Lung Cancer](#) Lingzhi Hong 1, Marcelo V Negrao 2, Seyedeh S Dibaj 3, et al. Runzhe Chen 2, Alexandre Reuben 2, Jadi M Bohac 2, Xiaoke Liu 2, Ferdinandos Skoulidis 2, Carl M G J Thorac Oncol. 2020 May 7;S1556-0864(20)30373-7. doi: 10.1016/j.jtho.2020.04.026. Online ahead of print.

**INTRODUCTION:** PD-L1 expression may vary in different disease sites and at different time points of disease course. We aimed to investigate PD-L1 heterogeneity and its impact on the predictive value on immune checkpoint inhibitor (ICI) therapy in NSCLC patients. **METHODS:** PD-L1 expression was analyzed in 1,398 NSCLC patients. The predictive value of PD-L1 on ICIs in 398 patients with metastatic NSCLC was assessed. **RESULTS:** PD-L1 was significantly associated with biopsy sites ( $P = 0.004$ ). Adrenal, liver and lymph node (LN) metastases had highest PD-L1 expression as a continuous variable and at 1% or 50% cutoff. PD-L1 expression was lower in bone and brain metastases. Among 112 patients with 2 specimens tested, 55 (49%) had major changes in PD-L1 falling into different clinically relevant categories ( $< 1\%$ ,  $1-49\%$ ,  $\geq 50\%$ ) at different time points. Prior ICI therapy was associated with significant decrease in PD-L1 compared to treatment-naïve counterparts ( $P = 0.015$ ). Patients with metastatic NSCLC treated with ICI ( $n = 398$ ) were divided into three cohorts based on biopsy sites: lung ( $n = 252$ ), LN ( $n = 85$ ) and distant metastasis (DM,  $n = 61$ ). Higher PD-L1 in lung or DM specimens was associated with significantly higher response rate, longer progression-free survival and overall survival. However, PD-L1 in LN biopsies was not associated with either response or survival. **CONCLUSION:** PD-L1 varies substantially across different anatomic sites and changes during clinical course. PD-L1 from different biopsy sites may have different predictive value for benefit from ICIs in NSCLC.

[A Phase II Study of Osimertinib for Patients With Radiotherapy-Naïve CNS Metastasis of Non-Small Cell Lung Cancer: Treatment Rationale and Protocol Design of the OCEAN Study \(LOGIK 1603/WJOG 9116L\)](#) Kazushige Wakuda 1, Hiroyuki Yamaguchi 2, Hirotsugu Kenmotsu 3, et al. BMC Cancer. 2020 May 1;20(1):370. doi: 10.1186/s12885-020-06874-6.

**BACKGROUND:** Patients with activating epidermal growth factor receptor (EGFR) mutations are highly responsive to EGFR-tyrosine kinase inhibitors (TKIs). However, it has been reported that approximately 15-30% of patients treated with EGFR-TKIs experience central nervous system (CNS) progression, and patients with EGFR mutations exhibit a higher incidence of brain metastasis than those without such mutations. The efficacy of osimertinib for treating CNS metastasis has been reported, but its efficacy for CNS metastasis in radiotherapy-naïve patients is unclear. **METHODS:** In the present prospective two-cohort phase II trial, 65 patients (T790M cohort, 40 patients; first-line cohort, 25 patients) with radiotherapy-naïve CNS metastasis of EGFR mutation-positive non-small cell lung cancer (NSCLC) will be included. Patients will be treated once-daily with osimertinib 80 mg. The primary endpoint is the response rate of brain metastasis as assessed using the PAREXEL criteria. Key secondary endpoints are progression-free survival and the response rate of brain metastasis as assessed using the RECIST criteria. We will exploratorily analyze the relationships of the blood concentration of osimertinib with its efficacy against brain metastasis of NSCLC and the accumulation of osimertinib in cerebrospinal fluid and evaluate tumor-derived DNA from plasma specimens for mutations in EGFR and other genes. Recruitment, which in October 2016, is ongoing. **DISCUSSION:** Although previous reports revealed the efficacy of osimertinib for CNS metastasis, these reports only involved subgroup analysis, and the efficacy of osimertinib for patients with previously untreated CNS metastasis remains unclear. The OCEAN study is the only trial of osimertinib for patients with untreated brain metastasis of NSCLC. This study should provide novel data about osimertinib. If the results of the OCEAN study are positive, then avoidance of radiotherapy will be recommended to patients harboring EGFR mutations and brain metastasis.

### [Efficacy of Immunotherapy Targeting the Neoantigen Derived From EGFR T790M/C797S Mutation in Non-Small Cell Lung Cancer](#)

Yu Akazawa<sup>1,2</sup>, Yuki Saito<sup>1</sup>, Toshiaki Yoshikawa et al. *Cancer Sci.* 2020 May 11. doi: 10.1111/cas.14451. Online ahead of print.

Lung cancer is the leading cause of cancer-related deaths worldwide. Epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) have often good clinical activity against non-small cell lung cancer (NSCLC) with activating EGFR mutations. Osimertinib, which is third-generation EGFR-TKI, provides clinical effect even on NSCLC harboring the threonine to methionine change at codon 790 of EGFR (EGFR T790M) mutation that cause TKI resistance. However, most NSCLC patients develop acquired resistance to Osimertinib within about one year, and 40% of these patients have the EGFR T790M and cysteine to serine change at codon 797 (C797S) mutations. Therefore, there is an urgent need for the development of novel treatment strategies for NSCLC patients with the EGFR T790M/C797S mutation. In this study, we novelty identified the EGFR T790M/C797S mutation-derived peptide (790-799) (MQLMPFGSLL) that binds the human leukocyte antigen (HLA)-A\*02:01, and successfully established EGFR T790M/C797S-peptide-specific cytotoxic T lymphocyte (CTL) clones from human peripheral blood mononuclear cells (PBMCs) of HLA-A2 healthy donors. One established CTL clone demonstrated adequate cytotoxicity against T2 cells pulsed with the EGFR T790M/C797S peptide. This CTL clone also had high reactivity against cancer cells that expressed an endogenously EGFR T790M/C797S peptide using an interferon- $\gamma$  (IFN- $\gamma$ ) enzyme-linked immunospot (ELISPOT) assay. In addition, we demonstrated using a mouse model that EGFR T790M/C797S peptide-specific CTLs were induced by EGFR T790M/C797S peptide vaccine in vivo. These findings suggest that an immunotherapy targeting a neoantigen derived from EGFR T790M/C797S mutation could be a useful novel therapeutic strategy for NSCLC patients with EGFR-TKI resistance, especially resistant to Osimertinib.



### [Radiation-Induced Secondary Cancer Risk Assessment in Patients With Lung Cancer After Stereotactic Body Radiotherapy Using the CyberKnife M6 System With Lung-Optimized Treatment](#)

Pei-Ju Chao 1 2 I-Hsing Tsai 1 Chun-Chieh Huang 2 , et al. *Front Bioeng Biotechnol.* 2020 May 7;8:306. doi: 10.3389/fbioe.2020.00306. eCollection 2020.

**BACKGROUND:** To evaluate the lifetime secondary cancer risk (SCR) of stereotactic body radiotherapy (SBRT) using the CyberKnife (CK) M6 system with a lung-optimized treatment (LOT) module for lung cancer patients. **METHODS:** We retrospectively enrolled 11 lung cancer patients curatively treated with SBRT using the CK M6 robotic radiosurgery system. The planning treatment volume (PTV) and common organs at risk (OARs) for SCR analysis included the spinal cord, total lung, and healthy normal lung tissue (total lung volume - PTV). Schneider's full model was used to calculate SCR according to the concept of organ equivalent dose (OED). **RESULTS:** CK-LOT-SBRT delivers precisely targeted radiation doses to lung cancers and achieves good PTV coverage and conformal dose distribution, thus posing limited SCR to surrounding tissues. The three OARs had similar risk equivalent dose (RED) values among four different models. However, for the PTV, differences in RED values were observed among the models. The cumulative excess absolute risk (EAR) value for the normal lung, spinal cord, and PTV was 70.47 (per 10,000 person-years). Schneider's Lnt model seemed to overestimate the EAR/lifetime attributable risk (LAR). **CONCLUSION:** For lung cancer patients treated with CK-LOT optimized with the Monte Carlo algorithm, the SCR might be lower. Younger patients had a greater SCR, although the dose-response relationship seemed to be non-linear for the investigated organs, especially with respect to the PTV. Despite the etiological association, the SCR after CK-LOT-SBRT for carcinoma and sarcoma, is low, but not equal to zero. Further research is required to understand and to show the lung SBRT SCR comparisons and differences across different modalities with motion management strategies.

### [Radiation Pneumonitis in Lung Cancer Patients Treated With Chemoradiation Plus Durvalumab](#)

Narek Shaverdian 1 , Maria Thor 2 , Annemarie F Shepherd 1 , et al. *Cancer Med.* 2020 May 6. doi: 10.1002/cam4.3113. Online ahead of print.

**INTRODUCTION:** Durvalumab after concurrent chemoradiation (cCRT) is now standard of care for unresected stage III non-small cell lung cancer (NSCLC). However, there is limited data on radiation pneumonitis (RP) with this regimen. Therefore, we assessed RP and evaluated previously validated toxicity models in predicting for RP in patients treated with cCRT and durvalumab. **METHODS:** Patients treated with cCRT and  $\geq 1$  dose of durvalumab were evaluated to identify cases of  $\geq$  grade 2 RP. The validity of previously published RP models was assessed in this cohort as well as a reference cohort treated with cCRT alone. The timing and incidence of RP was compared between cohorts. **RESULTS:** In total, 11 (18%) of the 62 patients who received cCRT and durvalumab developed  $\geq$  grade 2 RP a median of 3.4 months after cCRT. The onset of RP among patients treated with cCRT and durvalumab was significantly longer vs the reference cohort (3.4 vs 2.1 months;  $P = .01$ ). Numerically more patients treated with cCRT and durvalumab developed RP than patients in the reference cohort (18% vs 9%,  $P = .09$ ). Among patients treated with cCRT and durvalumab, 82% ( $n = 9$ ) were responsive to treatment with high-dose glucocorticoids. Previously published RP models widely underestimated the rate of RP in patients treated with cCRT and durvalumab [AUC  $\sim$  0.50;  $p(\text{Hosmer-Lemeshow})$ : 0.98-1.00]. **CONCLUSIONS:** Our data suggest a delayed onset of RP in patients treated with cCRT and durvalumab vs cCRT alone, and for RP to develop in a greater number of patients treated with cCRT and durvalumab. Previously published RP models significantly underestimate the rate of symptomatic RP among patients treated with cCRT and durvalumab.

[Cardiovascular Mortality and Morbidity Following Radical Radiotherapy for Lung Cancer: Is Cardiovascular Death Under-Reported?](#) F Sun 1, K Franks 2, L Murray 3, J Lilley 4, B Wheller 5, K Banfill 6, A McWilliam 7, A Abravan 8, M Van Herk 9, C Faivre-Finn 10, R Cubbon 11. Lung Cancer. 2020 May 13;146:1-5. doi: 10.1016/j.lungcan.2020.05.004. Online ahead of print.

**BACKGROUND:** Lung cancer is the most common malignancy worldwide. Radical radiotherapy is an essential treatment in the management of early and locally advanced lung cancer. Cardiac events are known to occur following radical radiotherapy for lung cancer. This study examines the burden of cardiac events post radiotherapy, and estimates the accuracy of death certification in patients who received radical radiotherapy for lung cancer. **METHODS:** We conducted a retrospective observational cohort study for all patients receiving radical radiotherapy for non-small cell lung cancer (NSCLC) at a large cancer centre between 01/01/2010 to 31/12/2016. Baseline cardiovascular disease and cancer status and treatment data were collected, along with hospital admission data and documented cause of death from the national registry for a median follow-up period of 34 months. **RESULTS:** Of 1224 patients included in the analysis, 378 (30.9%) patients had cardiovascular disease at baseline, including 140 (11.4%) with prior myocardial infarction. In the 846 patients without known cardiovascular disease, 451 (53.3%) had a QRISK2 predicted 10-year cardiovascular risk >20% over 10 years. During follow-up, 215 hospitalisations occurred (Incidence rate 6.2 per hundred patient years) which were classified as primarily cardiac, and 622 patients died (18 per 100 patient-years). However, death certificates stated a primary cardiac cause of death in only 33 cases (5.3% of deaths). Notably, 29% of patients dying out of hospital and certified as cancer death did not have documented cancer relapse prior to death, and 61% had no community palliative care input prior to death, implying these events may have been sudden and unexpected. **CONCLUSION:** There is a high prevalence of baseline cardiovascular disease in people undergoing radiotherapy for NSCLC, accompanied by significant rates of post-radiotherapy cardiovascular hospitalisation. However, only a small proportion of deaths are attributed to cardiovascular disease, together with the large amount of sudden deaths observed, this suggests that cardiovascular death is greatly under-reported in official statistics.

[Stereotactic Body Radiation Therapy for Early-Stage Non-Small-Cell Lung Cancer in Octogenarians and Older: An Alternative Treatment](#) Yanping Bei 1 2, Naoya Murakami 1, Yuko Nakayama 1, et al. J Radiat Res. 2020 May 8;rraa027. doi: 10.1093/jrr/rraa027. Online ahead of print. Surgery is the standard modality for early-stage I-II non-small-cell lung cancer (NSCLC). Generally, patients who are >80 years old tend to have more comorbidities and inferior physical status than younger patients. Stereotactic body radiation therapy (SBRT) may provide an alternative treatment for this group of patients. Here, we report our experience using SBRT to in the management of early-stage NSCLC in patients >80 years old. Patients aged ≥80 years old who were diagnosed with early-stage NSCLC and treated with definitive lung SBRT from January 2000 to January 2018 were retrospectively analysed. Local recurrence-free survival (LRFS), regional recurrence-free survival (RRFS), cancer-specific survival (CSS), progression-free survival (PFS), overall survival (OS) and treatment-related toxicities were analysed for patients >80 years old. A total of 153 patients were included, with a median age of 85 years (range, 80-94). The median follow-up period and OS was 39.8 months (range, 10-101 months) and 76 months, respectively. The 3-year OS, PFS, CSS, RRFS and LRFS were 65.3, 58.0, 75.7, 73.9 and 85.3%, respectively. Radiation pneumonitis grade 0-1, grade 2, grade 3 and grade 4 was observed in 135 (88.2%), 13 (8.5%), 4 (2.61%) and 1 (0.6%) patient(s), respectively. On multivariate analyses, tumor size, pretreatment C-reactive protein (CRP) value, histology and pretreatment physical state were significantly associated with OS. Definitive lung SBRT appears to have high LRFS and OS without causing high-grade radiation-related toxicities in early-stage NSCLC patients who were >80 years old.

**[Radiotranscriptomics Signature-Based Predictive Nomograms for Radiotherapy Response in Patients With Nonsmall Cell Lung Cancer: Combination and Association of CT Features and Serum miRNAs Levels](#)**

Liyuan Fan 1 2, Qiang Cao 3 Xiuping Ding 2, Dongni Gao 1, Qiwei Yang 1, Baosheng Li 2. *Cancer Med.* 2020 May 27. doi: 10.1002/cam4.3115. Online ahead of print.

**PURPOSE:** We aimed to establish radiotranscriptomics signatures based on serum miRNA levels and computed tomography (CT) texture features and develop nomogram models for predicting radiotherapy response in patients with nonsmall cell lung cancer (NSCLC). **METHODS:** We first used established radioresistant NSCLC cell lines for miRNA selection. At the same time, patients (103 for training set and 71 for validation set) with NSCLC were enrolled. Their pretreatment contrast-enhanced CT texture features were extracted and their serum miRNA levels were obtained. Then, radiotranscriptomics feature selection was implemented with the least absolute shrinkage and selection operator (LASSO), and signatures were generated by logistic or Cox regression for objective response rate (ORR), overall survival (OS), and progression-free survival (PFS). Afterward, radiotranscriptomics signature-based nomograms were constructed and assessed for clinical use. **RESULTS:** Four miRNAs and 22 reproducible contrast-enhanced CT features were used for radiotranscriptomics feature selection and we generated ORR-, OS-, and PFS- related radiotranscriptomics signatures. In patients with NSCLC who received radiotherapy, the radiotranscriptomics signatures were independently associated with ORR, OS, and PFS in both the training (OR: 2.94,  $P < .001$ ; HR: 2.90,  $P < .001$ ; HR: 3.58,  $P = .001$ ) and validation set (OR: 2.94,  $P = .026$ ; HR: 2.14,  $P = .004$ ; HR: 2.64,  $P = .016$ ). We also obtained a satisfactory nomogram for ORR. The C-index values for the ORR nomogram were 0.86 [95% confidence interval (CI), 0.75 to 0.92] in the training set and 0.81 (95% CI, 0.69 to 0.89) in the validation set. The calibration-in-the-large and calibration slope performed well. Decision curve analysis indicated a satisfactory net benefit.

**CONCLUSIONS:** The radiotranscriptomics signature could be an independent biomarker for evaluating radiotherapeutic responses in patients with NSCLC. The radiotranscriptomics signature-based nomogram could be used to predict patients' ORR, which would represent progress in individualized medicine.

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**SMALL CELL LUNG CANCER - SCLC**

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**[Rationale and Protocol Design for the TORG1835/NEXT-SHIP Study: A Phase II Study of Carboplatin, Etoposide and Nintedanib for Unresectable Limited/Extensive Disease Small Cell Lung Cancer With Idiopathic Pulmonary Fibrosis](#)**

Satoshi Ikeda 1, Takashi Ogura 2, Terufumi Kato 3, et al. *Ther Adv Med Oncol.* 2020 May 18;12:1758835920923431. doi: 10.1177/1758835920923431. eCollection 2020.

**BACKGROUND:** Interstitial pneumonia (IP) is one of the most common and poor prognostic comorbidities in patients with small cell lung cancer (SCLC). The pharmacotherapy for SCLC occasionally induces fatal acute exacerbation of comorbid IP, especially in patients with idiopathic pulmonary fibrosis (IPF). Safe and effective pharmacotherapy is of greater importance in patients with SCLC and IPF, because SCLC presents a poor prognosis without systemic treatment. Nintedanib is expected to restrain acute exacerbation and present angiogenesis-inhibiting effects. **METHODS:** The TORG1835/NEXT-SHIP study is the world's first multi-center, single-arm, phase II trial for unresectable limited or extensive disease SCLC with IPF. The patients receive carboplatin (area under the curve 5, day 1), etoposide (<75 years old: 100 mg/m<sup>2</sup>; ≥75 years old: 80 mg/m<sup>2</sup>; days 1-3), and nintedanib (150 mg twice a day) every 3 weeks for four cycles. After completion or discontinuation of carboplatin plus etoposide, the patients continue nintedanib until the discontinuation criteria are met. The primary endpoint is the incidence of acute exacerbation of IPF at 28 days after last administration of cytotoxic anti-cancer agents. We set an expected value of 5% and a threshold value of 20%. Taking statistical points (a/b errors: 0.05/0.75) and ineligible patients into account, the sample size was set at 33. The key secondary endpoints are time to first acute exacerbation of IPF, overall response rate, progression-free survival, overall

survival, and toxicities. **DISCUSSION:** Because there is no clinical trial for unresectable SCLC with IPF, our study would provide a major impact on clinical practice.

**Once Daily Versus Twice-Daily Radiotherapy in the Management of Limited Disease Small Cell Lung Cancer - Decision Criteria in Routine Practice**

Markus Glatzer 1, Corinne Faivre-Finn 2, Dirk De Ruysscher 3, et al. *Radiother Oncol.* 2020 May 21;S0167-8140(20)30246-2. doi: 10.1016/j.radonc.2020.05.004. Online ahead of print.

**BACKGROUND:** In limited disease small cell lung cancer (LD-SCLC), the CONVERT trial has not demonstrated superiority of once-daily (QD) radiotherapy (66 Gy) over twice-daily (BID) radiotherapy (45 Gy). We explored the factors influencing the selection between QD and BID regimens.

**METHODS:** Thirteen experienced European thoracic radiation oncologists as selected by the European Society for Therapeutic Radiation Oncology (ESTRO) were asked to describe their strategies in the management of LD-SCLC. Treatment strategies were subsequently converted into decision trees and analysed for agreement and discrepancies. **RESULTS:** Logistic reasons, patients' performance status and radiotherapy dose constraints were the three major decision criteria used by most experts in decision making. The use of QD and BID regimens was balanced among European experts, but there was a trend towards the BID regimen for fit patients able to travel twice a day to the radiotherapy site.

**CONCLUSION:** BID and QD radiotherapy are both accepted regimens among experts and the decision is influenced by pragmatic factors such as availability of transportation.

**Inhibition of p62/SQSTM1 Sensitizes Small-Cell Lung Cancer Cells to Cisplatin-Induced Cytotoxicity by Targeting NEDD9 Expression**

Lingzhi Xu 1, Fan Xu 1, Qingxia Kong 1, et al. *Mol Carcinog.* 2020 May 19. doi: 10.1002/mc.23215. Online ahead of print.

Drug resistance is the leading cause for rapid progression and relapse in small-cell lung cancer (SCLC) patients. Thus overcoming drug resistance still remains to be urgently resolved during SCLC treatment. Here, we found p62/SQSTM1 was enriched in SCLC spheroids, a subpopulation possessing cancer stem-like properties, which is responsible for cancer relapse and metastasis. Subsequent functional assays in vitro showed that short hairpin RNA (shRNA)-mediated p62 knockdown increased sensitivity of SCLC cell lines to cisplatin (DDP), whereas lentivirus-mediated p62 ectopic overexpression diminished DDP-induced cytotoxicity in both NCI-H446 and NCI-H1688 cell lines. Moreover, ectopic p62 overexpression promoted DDP resistance of NCI-H446 cells-derived tumor xenografts in immunodeficient mice in vivo, as indicated by accelerated tumor growth rate and reduced fluorescent activity of cleaved caspase-3. Gene expression profiling analysis revealed that p62 was positively correlated with neuronal precursor cell-expressed, developmentally downregulated gene 9 (NEDD9) expression level. Consistently, NEDD9 messenger RNA (mRNA) level was decreased upon p62 suppression by small interfering RNA (siRNA) and increased with p62 transient overexpression in SCLC cell lines, suggesting that p62 positively regulated NEDD9 mRNA. Depletion of NEDD9 by siRNA, to a large extent, reversed p62-overexpressed SCLC cells to DDP-induced cytotoxicity, implying NEDD9 might act as a downstream target which was in charge of p62-mediated DDP resistance. Taken together, our findings uncovered a previously unknown role of p62 in the regulation of SCLC drug resistance, assigning p62 as an attractive target for SCLC treatment.

[The Role of Malnutrition and Muscle Wasting in Advanced Lung Cancer](#) Rishi Jain 1 , Chris Coss 2 Peter Whooley 2, Mitch Phelps 2, Dwight H Owen 4 *Curr Oncol Rep.* 2020 May 15;22(6):54. doi: 10.1007/s11912-020-00916-9.

**PURPOSE OF REVIEW:** Malnutrition, cancer cachexia, and sarcopenia often co-occur in patients with advanced cancer and are associated with poorer response to chemotherapy and reduced survival. Here, we evaluate the current literature regarding the role of nutrition and these associated conditions in patients with advanced lung cancer. **RECENT FINDINGS:** While rates of malnutrition are high, nutritional intervention studies have generally been limited by small sample sizes. Novel strategies such as home-based meal delivery may have promise. While no therapy is approved for cancer cachexia, ghrelin agonists and other targeted therapies have yielded promising data in clinical trials. Recent data also suggest that obesity may improve immunotherapy responsiveness. Malnutrition and associated muscle wasting are clearly negative prognostic markers in advanced lung cancer. Patients with malnutrition should be urgently referred for dietary counseling and guidelines for nutritional support should be followed. Optimal treatment of these syndromes will likely include nutrition and anti-cachexia interventions used in combination.

[Genetic Polymorphisms and Haplotypes of BRCA1 Gene Associated With Quality of Life and Survival Among Patients With Non-Small-Cell Lung Cancer](#)

Tong Su 1 , Hao Sun , Xiaofang Lu 4, Chen 1 , Lei Xiao , Jingwen H 1, Yang Yang 5, Yunxiang Tang 6 7 *Qual Life Res.* 2020 May 18. doi: 10.1007/s11136-020-02509-2. Online ahead of print.

**PURPOSE:** Quality of life (QoL) and prognosis of lung cancer (LC) patients are poor. Previous studies focused less on the relationship between genetic factors and the QoL of LC patients. The current study is intended to explore the association of SNPs and haplotypes of BRCA1 and the QoL and survival of patients with LC. **METHODS:** QOL of 291 non-small-cell LC patients was measured by EORTC Core Quality of Life Questionnaire (QLQ-C30) and EORTC Quality of Life Questionnaire-Lung Cancer 13 (QLQ-LC13) before discharge. Three tag SNPs of the BRCA1 gene (rs1799966, rs3737559, rs8067269) were detected using an improved multiplex ligation detection reaction (iMLDR) technique. Haplotype analysis was conducted using the software Haploview 4.2. The patients' survival was followed up every six months until March 2019. **RESULTS:** rs8067269 was associated with physical functioning ( $\beta = 7.97$ ,  $p = 0.024$ ) and diarrhea (Odds ratios (OR) 0.32,  $p = 0.042$ ). rs1799966-rs3737559-rs8067269 haplotype was associated with several domains of QoL, including physical functioning (TCG vs. CCA:  $\beta = 6.21$ ,  $p = 0.010$ ), worse dyspnea (TCG vs. CTA: OR 2.05,  $p = 0.031$ ) and peripheral neuropathy (TCG vs. CTA: OR 3.91,  $p = 0.030$ ). BRCA1 rs1799966 CC genotype, rs8067269 AA genotype and CCA haplotype were associated with longer survival time of LC patients ( $p < 0.05$ ). **CONCLUSION:** SNPs and haplotypes of BRCA1 gene were associated with the QoL and survival of patients with LC. Patients with certain genotypes and haplotypes (i.e., rs8067269 AA genotype, or CCA haplotype) had better QoL and prognosis.

[Exercise Prescription for Symptoms and Quality of Life Improvements in Lung Cancer Patients: A Systematic Review](#)

Alberto Codima 1, Willian das Neves Silva 1 2 , Ana Paula de Souza Borges 1 2 , **PURPOSE:** The purpose of this study was to conduct a systematic review to assess the effect of exercise on symptoms and quality of life in lung cancer patients. **METHODS:** We conducted a systematic review using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. PubMed, Medline, Embase, Scopus, Web of Science, and SciELO were searched for studies published from January 1998 to January 2019. The review included all randomized controlled trials that evaluated the

effect of exercise on symptoms and quality of life of lung cancer patients. Two reviewers independently assessed the quality of all the included studies using the Physiotherapy Evidence Database scale.

**RESULTS:** In total, ten studies (835 participants) met all inclusion criteria. Three studies investigated the effect of exercise after lung resection, whereas four studies investigated it as a pre-surgery intervention. Two studies investigated the effect of exercise in patients under systemic treatment only, and one study included patients on diverse treatment plans. Exercise protocols consisted of different combinations of strength, aerobic, and inspiratory muscle training. Two trials, including 101 participants, found significant difference in quality of life between groups, favoring the intervention group; and five trials, including 549 participants, found significant inter-group differences in isolated symptoms, also favoring the intervention group. **CONCLUSIONS:** Exercise can lead to improvements of symptoms and of quality of life in lung cancer survivors. Providing resistance training combined with high-intensity interval aerobic exercise after lung resection seems to be particularly effective. Further studies are warranted to investigate exercise for patients with poor performance status.

### **Evaluation of Nutritional Status in Non-Small-Cell Lung Cancer: Screening, Assessment and Correlation With Treatment Outcome**

Ilaria Trestini<sup>1</sup>, Isabella Sperduti<sup>2</sup>, Marco Sposito<sup>1</sup>, et al. ESMO Open. 2020 May;5(3):e000689. doi: 10.1136/esmopen-2020-000689.

**BACKGROUND:** Nutritional derangements are common hallmarks of non-small-cell lung cancer (NSCLC). Nevertheless, their early detection is overlooked in clinical routine. This study aimed to evaluate nutritional status and its correlation with outcome in NSCLC patients. **METHODS/DATA:** regarding NSCLC patients undergoing nutritional evaluation were prospectively collected (May 2016-October 2018). Nutritional risk was assessed by Nutritional Risk Screening 2002 (NRS-2002). Bilateral psoas major muscles were measured at L3 vertebrae level with routine staging-computed tomography and changes were evaluated using Wilcoxon signed-rank test. Clinico-pathological and nutritional data were correlated to progression-free/overall survival (PFS/OS) and response rate (ORR) using a Cox and logistic regression model. Kaplan-Meier curves were compared with log-rank test. **RESULTS:** Thirty-eight patients were included. The majority (65.8%) of them were at nutritional risk (NRS-2002  $\geq 3$ ). At multivariate analysis for patients with advanced disease, age (HR 2.44,  $p=0.05$ ), performance status (HR 2.48,  $p=0.043$ ) and NRS-2002 (HR 1.74,  $p=0.001$ ) were significant independent predictors for PFS and weight loss (HR 1.07,  $p=0.008$ ) for OS. Patients with baseline NRS-2002  $< 3$  had significantly longer 1-year PFS (85.7% vs 19.4%,  $p=0.02$ ) and higher ORR (66.7% vs 21.4%) than those with NRS-2002  $\geq 3$ . An explorative evaluation demonstrated that NRS-2002 score significantly decreased after nutritional intervention ( $p=0.001$ ) for 3 months. **CONCLUSION:** Baseline nutritional risk represents a prognostic factor in NSCLC. Nutritional counselling should be applied as a fundamental tool to improve nutritional risk in a short period, ameliorating patients' outcome.

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## **COMPLEMENTARY & ALTERNATIVE THERAPY**

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### **Evaluation of Anticancer Effects of a Pharmaceutically Viable Extract of a Traditional Polyherbal Mixture Against Non-Small-Cell Lung Cancer Cells**

Varuni Colamba Pathiranage<sup>1</sup>, Ira Thabrew<sup>1</sup>, Sameera R Samarakoon<sup>2</sup>, Kamani H Tennekoon<sup>1</sup>, Umapriyatharshini Rajagopalan<sup>1</sup>, Meran K Ediriweera<sup>1</sup>. Affiliations J Integr Med. 2020 May;18(3):242-252. doi: 10.1016/j.joim.2020.02.007. Epub 2020 Feb 20.

**OBJECTIVE:** The present work tested organic solvents to prepare an extract with anticancer properties from a polyherbal mixture containing *Nigella sativa* (seeds), *Hemidesmus indicus* (roots) and *Smilax glabra* (rhizomes). We evaluate anticancer effects in non-small-cell lung cancer cells (NCI-H292), and discuss optimization for pharmaceutical use in the context of efficacy, yield and toxicity. **METHODS:** Using different organic solvents, six extracts were prepared from the polyherbal mixture. Based on the

cytotoxic effects of these extracts on NCI-H292 cells and normal lung cells (MRC-5), as evaluated by the sulphorhodamine B assay, the total ethyl acetate (T-EA) extract was selected for further analysis. The possible anticancer mechanisms were assessed by evaluating the extract's effects on apoptosis (through fluorescent microscopic analysis, DNA fragmentation analysis, caspase 3/7 assay and analysis of expression levels of apoptosis-related genes p53, Bax, survivin, Hsp70 and Hsp90), colony formation and antioxidant activity. **RESULTS:** The extract had cytotoxic effects against NCI-H292 cells in a time- and dose-dependent manner. Significant antioxidant activity and inhibition of colony formation were also observed. The expression level of caspase 3/7 significantly ( $P < 0.001$ ) increased in NCI-H292 cells treated with 50  $\mu\text{g/mL}$  of the extract. The same dosage led to a significant increase in expression levels of Bax and p53 ( $P < 0.05$  and  $P < 0.01$  respectively), accompanied by a significant decrease ( $P < 0.0001$ ) in survivin, Hsp70 and Hsp90. **CONCLUSION:** T-EA extract of the above polyherbal mixture has cytotoxicity against NCI-H292 cells via induction of apoptosis, antioxidant effects and inhibition of colony formation.

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## MISCELLANEOUS WORKS

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[Sex-specificity in Lung Cancer Risk](#) Claudia Stapelfeld 1, Christine Dammann 1, Edmund Maser 1 Int J Cancer. 2020 May 1;146(9):2376-2382. doi: 10.1002/ijc.32716.

Smoking is indisputably linked to lung cancer, yet only a small fraction of smokers develops this disease. Although previously tobacco-derived carcinogens and enzyme polymorphisms have been identified to increase the risk for smokers, recent epidemiological data suggest even sex-specificity as a new and additional factor. Obviously, women have a higher risk to develop lung cancer upon smoking than men. Overall, the odds ratio to develop lung cancer was almost three times greater for women than for men, DNA adduct levels were higher among females than in males and mutations in the tumor suppressor gene p53 and the proto-oncogene K-RAS were more frequently found in women than in men. A growing number of studies suggest that the interaction between tobacco carcinogens and endogenous and exogenous sex steroids may be important. Women taking hormone replacement therapy (HRT) or oral contraceptives experienced to have an increased lung cancer incidence. Epidemiologic data on HRT show a significant association between both a younger median age at lung cancer diagnosis and a shorter median survival time. Another clue is the significantly higher number of lung cancer diagnosed women who are largely premenopausal in comparison to diagnosed men in the same age or women with shorter menstrual cycles. Finally, the Coronary Drug Project (men who received estrogen preparations to reduce future cardiac events) was stopped when increased lung cancer mortality was observed in the estrogen therapy group. The present review provides a short overview and discussion on lung cancer risk and the impact thereon of sex.

[Smoking Is Associated With Pneumonia Development in Lung Cancer Patients](#) Jung Won Heo 1 , Chang Dong Yeo 1 , Chan Kwon Park 2, et al. BMC Pulm Med. 2020 May 1;20(1):117. doi: 10.1186/s12890-020-1160-8.

**BACKGROUND:** Various host factors can promote pneumonia susceptibility of lung cancer patients. However, data about risk factors for pneumonia in lung cancer patients receiving active treatments such as chemotherapy, radiotherapy, and surgical intervention are limited. Thus, the purpose of this study was to identify risk factors for pneumonia development in lung cancer patients. **METHODS:** The present study used a lung cancer cohort of the Catholic Medical Center at the Catholic University of Korea from January 2015 to December 2018. Pneumonia was defined by the presence of a new or progressive infiltration on chest imaging together with any of the following: new onset purulent sputum, change in character of chronic sputum, and fever. We ruled out noninfectious infiltration such as drug or radiation toxicity and hydrostatic pulmonary edema. We especially excluded those if computed tomography

revealed sharp demarcation consolidation or ground glass opacity limited radiation field. **RESULTS:** A total of 413 patients were enrolled in this study. Pneumonia occurred in 118 (28.6%) patients. The pneumonia group had significantly worse overall survival (OS) than the non-pneumonia group ( $456.7 \pm 35.0$  days vs.  $813.4 \pm 36.1$  days, log rank  $p < 0.001$ ). In patients with pneumonia, OS was shorter in ex-smokers and current smokers than in never smokers ( $592.0 \pm 101.0$  days vs.  $737.0 \pm 102.8$  days vs.  $1357.0$  days, log rank  $p < 0.001$ ). Age (hazard ratio [HR]: 1.046; 95% confidence interval [CI]: 1.019-1.074;  $p = 0.001$ ), clinical stage IV (HR: 1.759; 95% CI: 1.004-3.083;  $p = 0.048$ ), neutropenia (HR: 2.620; 95% CI: 1.562-4.396;  $p < 0.001$ ), and smoking (HR: 2.040; 95% CI: 1.100-3.784;  $p = 0.024$ ) were independent risk factors of pneumonia development in lung cancer patients in multivariate analysis. In subgroup analysis for patients treated with chemotherapy, age (HR: 1.043; 95% CI: 1.012-1.074;  $p = 0.006$ ), neutropenia (HR: 3.199; 95% CI: 1.826-5.605;  $p < 0.001$ ), and smoking (HR: 2.125; 95% CI: 1.071-4.216;  $p = 0.031$ ) were independent risk factors of pneumonia development. **CONCLUSIONS:** Smoking and neutropenia were risk factors affecting pneumonia development in the total group and subgroup of patients with lung cancer.

### [Treatment Guidance for Patients With Lung Cancer During the Coronavirus 2019 Pandemic](#)

Anne-Marie C Dingemans 1, Ross A Soo 2, Abdul Rahman Jazieh 3, J Thorac Oncol. 2020 May 15;S1556-0864(20)30382-8. doi: 10.1016/j.jtho.2020.05.001. Online ahead of print.

The global coronavirus disease 2019 pandemic continues to escalate at a rapid pace inundating medical facilities and creating substantial challenges globally. The risk of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in patients with cancer seems to be higher, especially as they are more likely to present with an immunocompromised condition, either from cancer itself or from the treatments they receive. A major consideration in the delivery of cancer care during the pandemic is to balance the risk of patient exposure and infection with the need to provide effective cancer treatment. Many aspects of the SARS-CoV-2 infection currently remain poorly characterized and even less is known about the course of infection in the context of a patient with cancer. As SARS-CoV-2 is highly contagious, the risk of infection directly affects the cancer patient being treated, other cancer patients in close proximity, and health care providers. Infection at any level for patients or providers can cause considerable disruption to even the most effective treatment plans. Lung cancer patients, especially those with reduced lung function and cardiopulmonary comorbidities are more likely to have increased risk and mortality from coronavirus disease 2019 as one of its common manifestations is as an acute respiratory illness. The purpose of this manuscript is to present a practical multidisciplinary and international overview to assist in treatment for lung cancer patients during this pandemic, with the caveat that evidence is lacking in many areas. It is expected that firmer recommendations can be developed as more evidence becomes available.

### [Could Venous Thromboembolism and Major Bleeding Be Indicators of Lung Cancer Mortality? A Nationwide Database Study](#)

Jennifer Howlett 1 2, Eric Benzenine 2 3, Jonathan Cottinet 2 3, Pascal Foucher 4, Philippe Fagnoni 1 5, Catherine Quantin 6 7 8 BMC Cancer. 2020 May 24;20(1):461. doi: 10.1186/s12885-020-06930-1.

**BACKGROUND:** Venous thromboembolism (VTE) is highly prevalent in cancer patients and can cause severe morbidity. VTE treatment is essential, but anticoagulation increases the risk of major bleeding. The purpose was to evaluate the impact of VTE and major bleeding on survival and to identify significant risk factors for these events in lung cancer patients. **METHODS:** Data were extracted from a permanent sample of the French national health information system (including hospital and out-of-hospital care) from 2009 to 2016. All episodes of VTE and major bleeding events within one year after cancer diagnosis were identified. A Cox model was used to analyse the effect of VTE and major bleeding on the patients' one-year survival. VTE and major bleeding risk factors were analysed with a Fine and Gray survival



model. **RESULTS:** Among the 2553 included patients with lung cancer, 208 (8%) had a VTE episode in the year following diagnosis and 341 (13%) had major bleeding. Almost half of the patients died during follow-up. Fifty-six (60%) of the patients presenting with pulmonary embolism (PE) died, 48 (42%) of the patients presenting with deep vein thrombosis (DVT) alone died and 186 (55%) of those presenting with a major bleeding event died. The risk of death was significantly increased following PE and major bleeding events. VTE concomitant with cancer diagnosis was associated with an increased risk of VTE recurrence beyond 6 months after the first VTE event (sHR = 4.07 95% CI: 1.57-10.52). Most major bleeding events did not appear to be related to treatment. **CONCLUSION:** VTE is frequent after a diagnosis of lung cancer, but so are major bleeding events. Both PE and major bleeding are associated with an increased risk of death and could be indicators of lung cancer mortality.

[Evidence That Established Lung Cancer Mortality Disparities in American Indians Are Not Due to Lung Cancer Genetic Testing and Targeted Therapy Disparities](#) Abbie Begnaud 1, Ping Yang 2, Camille Robichaux 3, Nathan Rubin 4, Robert Kratzke 1, Anne Melzer 5, Constantin Aliferis 1, Pamala Jacobson 6 Clin Lung Cancer. 2020 May;21(3):e164-e168. doi: 10.1016/j.clcc.2019.10.012. Epub 2019 Oct 30.

**BACKGROUND:** American Indians and Alaska Natives (AI/AN) continue to experience extreme lung cancer health disparities. The state of Minnesota is home to over 70,000 AI/AN, and this population has a 2-fold increase in lung cancer mortality compared to other races within Minnesota. Genetic mutation testing in lung cancer is now a standard of high-quality lung cancer care, and EGFR mutation testing has been recommended for all adenocarcinoma lung cases, regardless of smoking status. However, genetic testing is a controversial topic for some AI/AN. **PATIENTS AND METHODS:** We performed a multisite retrospective chart review funded by the Minnesota Precision Medicine Grand Challenge as a demonstration project to examine lung cancer health disparities in AI/AN. We sought to measure epidemiology of lung cancer among AI receiving diagnosis or treatment in Minnesota cancer referral centers as well as rate of EGFR testing. The primary outcome was the rate of EGFR mutational analysis testing among cases and controls with nonsquamous, non-small-cell lung cancer. We secured collaborations with 5 health care systems covering a diverse geographic and demographic population. **RESULTS:** We identified 200 cases and 164 matched controls from these sites. Controls were matched on histology, smoking status, sex, and age. In both groups, about one third of subjects with adenocarcinoma received genetic mutation testing. **CONCLUSION:** There was no significant difference in mutation testing in AI compared to non-AI controls at large health care systems in Minnesota. These data indicate that other factors are likely contributing to the higher mortality in this group.

[Smoking Is Associated With Pneumonia Development in Lung Cancer Patients](#) Jung Won Heo 1, Chang Dong Yeo 1, Chan Kwon Park 2, et al. BMC Pulm Med. 2020 May 1;20(1):117. doi: 10.1186/s12890-020-1160-8. Hye Seon Kang 8

**BACKGROUND:** Various host factors can promote pneumonia susceptibility of lung cancer patients. However, data about risk factors for pneumonia in lung cancer patients receiving active treatments such as chemotherapy, radiotherapy, and surgical intervention are limited. Thus, the purpose of this study was to identify risk factors for pneumonia development in lung cancer patients. **METHODS:** The present study used a lung cancer cohort of the Catholic Medical Center at the Catholic University of Korea from January 2015 to December 2018. Pneumonia was defined by the presence of a new or progressive infiltration on chest imaging together with any of the following: new onset purulent sputum, change in character of chronic sputum, and fever. We ruled out noninfectious infiltration such as drug or radiation toxicity and hydrostatic pulmonary edema. We especially excluded those if computed tomography revealed sharp demarcation consolidation or ground glass opacity limited radiation field. **RESULTS:** A total of 413 patients were enrolled in this study. Pneumonia occurred in 118 (28.6%) patients. The

pneumonia group had significantly worse overall survival (OS) than the non-pneumonia group ( $456.7 \pm 35.0$  days vs.  $813.4 \pm 36.1$  days, log rank  $p < 0.001$ ). In patients with pneumonia, OS was shorter in ex-smokers and current smokers than in never smokers ( $592.0 \pm 101.0$  days vs.  $737.0 \pm 102.8$  days vs.  $1357.0$  days, log rank  $p < 0.001$ ). Age (hazard ratio [HR]: 1.046; 95% confidence interval [CI]: 1.019-1.074;  $p = 0.001$ ), clinical stage IV (HR: 1.759; 95% CI: 1.004-3.083;  $p = 0.048$ ), neutropenia (HR: 2.620; 95% CI: 1.562-4.396;  $p < 0.001$ ), and smoking (HR: 2.040; 95% CI: 1.100-3.784;  $p = 0.024$ ) were independent risk factors of pneumonia development in lung cancer patients in multivariate analysis. In subgroup analysis for patients treated with chemotherapy, age (HR: 1.043; 95% CI: 1.012-1.074;  $p = 0.006$ ), neutropenia (HR: 3.199; 95% CI: 1.826-5.605;  $p < 0.001$ ), and smoking (HR: 2.125; 95% CI: 1.071-4.216;  $p = 0.031$ ) were independent risk factors of pneumonia development.

**CONCLUSIONS:** Smoking and neutropenia were risk factors affecting pneumonia development in the total group and subgroup of patients with lung cancer.

[Primary Lung Cancer Diagnoses in People Living With HIV in a Large Clinical Centre in Montreal, Canada Over 3 Decades](#) Béatrice Bichara 1, Jean-Pierre Routy 2 3, Nicole Ezer 4 5, Cecilia T Costiniuk 2 6 AIDS Care. 2020 May 6;1-5. doi: 10.1080/09540121.2020.1758614. Online ahead of print.

Lung cancer is the most frequent type of cancer-related death in people living with HIV (PLWH). We conducted a review of primary lung cancers in PLWH at the McGill University Health Centre from 1988-May 2018 to understand potential factors contributing to their development prior to the implementation of a lung cancer screening program. Twenty-seven individuals had a diagnosis of a lung tumor. Of these individuals, 21 (78%) had a primary lung cancer, over 21,428 person-years follow-up. Median age was 54.5 years [25th and 75th percentiles 49.0, 62.0]. Median CD4 count was 185.0 cells/ $\mu$ L [25th and 75th percentiles 54.0, 446.0] and 52% were on antiretroviral therapy with suppressed viral loads. Type of primary lung cancer included: non-small cell lung cancer ( $n = 15$ ), small-cell lung cancer ( $n = 4$ ) and bronchial carcinomas ( $n = 2$ ). Metastatic disease at diagnosis was present in 11 (52%) persons. Survival was a median of 7.5 months from the time of diagnosis [25th and 75th percentiles 2.0, 9.0]. In conclusion, we observed a high proportion of lung cancers detected at very late stages of disease and with metastatic involvement. The implementation of a lung cancer screening program in 2018 should set a stage shift for earlier diagnosis and treatment.

[Lung Cancer Incidence and Mortality in Relationship to Hormone Replacement Therapy Use Among Women Participating in the PLCO Trial: A Post Hoc Analysis](#) Omar Abdel-Rahman 1 2

Int J Clin Oncol. 2020 May;25(5):885-891. doi: 10.1007/s10147-020-01615-y. Epub 2020 Jan 9.

**OBJECTIVE:** To evaluate the impact of hormone replacement therapy (HRT) on the incidence and mortality of lung cancer among female participants in the prostate, lung, colorectal, and ovary (PLCO) trial. **METHODS:** All women participating in the PLCO trial with complete information about HRT exposure were included in the current analysis. All study population were aged 55-74 years without prior history of lung cancer at the time of study enrollment. Multivariate Cox regression analysis was used to evaluate the impact of HRT exposure on lung cancer incidence and mortality. For both end points, the model was adjusted for: age, body mass index, study arm, race, cigarette smoking and family history of lung cancer. **RESULTS:** A total of 77,911 female participants were included in the current analysis, including 27,663 participants who never used HRT before inclusion into the PLCO trial and 50,248 participants who used some form of HRT before inclusion into the PLCO trial. Prior exposure to HRT seems to be protective against the development of lung cancer in a multivariate analysis (hazard ratio for ever exposure versus never exposure 0.876; 95% CI 0.783-0.981;  $P = 0.022$ ). Similarly, prior exposure to HRT seems also to be protective against death from lung cancer in a multivariate analysis (hazard ratio for ever exposure versus never exposure 0.814; 0.709-0.934;  $P = 0.003$ ). Further multivariate Cox

regression analysis showed that current HRT usage at the time of PLCO trial entry (and not former HRT usage) seemed to be protective against lung cancer development (hazard ratio for current versus never users 0.842; 0.743-0.954;  $P = 0.007$ ) and lung cancer-specific mortality (hazard ratio for current versus never users 0.800; 0.686-0.932;  $P = 0.004$ ). **CONCLUSION:** HRT use at the time of PLCO trial entry seems to be associated with lower probability of lung cancer development and death. Further studies are needed to elucidate the biological mechanisms behind this observation.

### **Lung Cancer Surgical Regionalization Disproportionately Worsens Travel Distance for Rural**

**Patients** Joshua N Herb<sup>1</sup>, Lisette N Dunham<sup>2</sup>, Gita Mody<sup>1</sup>, Jason M Long<sup>1</sup>, Karyn B Stitzenberg<sup>1</sup>. *J Rural Health*. 2020 May 1. doi: 10.1111/jrh.12440. Online ahead of print.

**PURPOSE:** Major cancer surgeries have regionalized to fewer and higher-volume hospitals, with the goal of improving the quality of surgical care. However, regionalization may have negative effects on geographic access to care. We hypothesize that lung cancer patients have been traveling further for surgery over time as regionalization has occurred, and this increased travel has primarily impacted rural patients. **METHODS:** A North Carolina all-payer state discharge database was used to capture discharges from 2005 to 2015 for patients undergoing lung cancer resection. Changes in patterns of care over time in high-volume centers (HVC) were examined. Adjusted patient straight-line travel distance was estimated over time and stratified by rural-urban location. **FINDINGS:** The number of hospitals performing lung cancer resections decreased from 49 to 31 over the study period ( $P = .0006$ ), and the proportion of patients receiving care at HVC increased from 23% to 44% ( $P < .0001$ ). Rural patient travel distance increased over time by 8.5 miles (95% CI: 0.56-17.10,  $P = .048$ ), from 45.1 to 53.6 miles. There was no change in urban patient travel distance. The difference in adjusted travel distance between rural and urban patients nearly doubled from 2005 to 2015 (9.6 to 17.9 miles,  $P < .0001$ ). **CONCLUSION:** In North Carolina, lung cancer surgical regionalization occurred over the study period and was accompanied by increases in travel distance for rural patients only. Further work is needed to determine the effects of greater travel distance on patterns of cancer care for rural patients.