Caring Ambassadors Lung Cancer Program
Literature Review, June 2020

BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES

Efficacy of Gefitinib Combined With 125 I Radioactive Particles in the Treatment of Transplanted Lung Cancer Tumors in Nude Mice Cardiovasc Intervent Radiol. 2020 Jun 30. doi: 10.1007/s00270-020-02550-1. Online ahead of print. Chaojie Li 1 , Linyan Yao 1 , Ju Gong 1 , Haopeng Pang 1 , Qungang Shan 1 , Ziyin Wang 1 , Jian Lu 2 , Zhongmin Wang 3

OBJECTIVE: To investigate the efficacy of gefitinib combined with iodine-125 (125I) radioactive particles in the treatment of transplanted tumors of the lung cancer cell line A549 in nude mice. **MATERIALS AND METHODS:** Twenty-four nude mice were inoculated with A549-luc human lung adenocarcinoma cells stably expressing luciferase. The tumor size was approximately 8-10 mm after 20 days. The mice were randomly divided into four groups: a control group (n = 6), an 125I particles group (n = 6), a gefitinib group (n = 6) and a gefitinib combined 125I particles implantation group (n = 6). Tumor growth was observed, and changes in tumor size were continuously measured. Bioluminescence imaging was used to detect the bioluminescence activity of human lung adenocarcinoma A549-luc cells containing the luciferase reporter gene in vivo. After 35 days, the nude mice were sacrificed, and a tumor growth curve was drawn. **RESULTS:** Before treatment, the tumor volumes of the four groups were not significantly different. The tumor volume difference was statistically significant in the four groups (control group, 125I radioactive particles, gefitinib group and combined drug group) at 5 weeks after treatment (F = 10.305, P < 0.05). The tumor size in the gefitinib combined with 125I particles group was significantly smaller than that in the gefitinib, 125I particles and control groups and significantly smaller than that before treatment. There was no significant difference in the bioluminescence signal intensity between the four groups before treatment. The numbers of biofluorescence photons difference were statistically significant in the four groups (F = 28.975, P < 0.05). The bioluminescence signal intensity in the gefitinib combined with 125I particles group was significantly lower than that in the 125I particles, gefitinib and control groups and significantly lower than that before treatment. **CONCLUSION:** Gefitinib combined with 125I radioactive particles brachytherapy can significantly inhibit tumor growth.

[miR-192-5p Upregulation Mediates the Suppression of Curcumin in Human NSCLC Cell Proliferation, Migration and Invasion by Targeting c-Myc and Inactivating the Wnt/β-catenin Signaling Pathway](#) Mol Med Rep. 2020 Jun 4. doi: 10.3892/mmr.2020.11213. Online ahead of print. Yancheng Pan 1 , Ying Sun 2 , Ziqi Liu 2 , Chao Zhang 1

Curcumin is a naturally active phenolic compound extracted from the rhizome of the plant Curcuma longa, which has been demonstrated to serve as an anticancer drug in different types of cancer, including non-small-cell lung cancer (NSCLC). Accumulating evidence has suggested that curcumin may exert epigenetic regulatory effects on microRNAs (miRs). Therefore, the present study aimed to investigate the role of miR-192-5p, and the effects of curcumin, in NSCLC, alongside the underlying mechanisms. Human NSCLC cells, A427 and A549, were treated with curcumin, and the expression levels of miR-192-5p and c-Myc were detected using reverse transcription-quantitative PCR and western blotting. Cellular proliferation was analyzed using Cell Counting Kit-8 assays and cell viability was determined using a MTT assay. Additionally, the migratory and invasive abilities of cells were analyzed using Transwell and Matrigel assays, respectively. The binding sites between miR-192-5p and c-Myc were predicted using TargetScanHuman software, and confirmed using a dual-luciferase reporter assay and RNA immunoprecipitation. Finally, the Wnt pathway regulator, β-catenin, and cyclin D1 expression levels were determined using western blotting. Curcumin treatment inhibited NSCLC cell proliferation, migration, invasion and viability in a dose-dependent manner, in addition to promoting a dose-dependent increase in the expression levels of miR-192-5p and a reduction in c-Myc expression levels. Notably, the genetic knockdown of miR-192-5p blocked the inhibitory effects of curcumin on NSCLC progression and instead promoted NSCLC progression, which was observed to be partially reversed by c-Myc silencing; thus, c-Myc was suggested to be a direct target gene of miR-192-5p as demonstrated by the TargetScanHuman database, dual-lucierase and RIP assay results. In addition, the curcumin-induced decreased expression levels of β-catenin, cyclin D1 and c-Myc were rescued following the genetic knockdown of miR-192-5p. In conclusion, these findings suggested that the upregulation of miR-192-5p may underlie the inhibitory effects of curcumin on NSCLC cells through targeting c-Myc and inactivating the Wnt/β-catenin signaling pathway.

[Impact of Pemetrexed Chemotherapy on the Gut Microbiota and Intestinal Inflammation of Patient-Lung-Derived Tumor Xenograft (PDX) Mouse Models](#) Sci Rep. 2020 Jun 4;10(1):9094. doi: 10.1038/s41598-020-65792-6. Cindy Pensec 1 2 , Florence Gillaizeau 1 , Dominique Guenot 2 3 , Anne Bessard 4 , Thomas Carton 1 2 , Sébastien Leuillet 1 2 , Mario Campone 5 , Michel Neunlist 4 , Hervé M Blottière 6 7 , Françoise Le Vacon 8 9

Chemotherapy remains the gold standard for advanced cancer. Pemetrexed, a chemotherapeutic agent used in non-small cell lung cancer, can induce significant side effects in patients. Although microbiota's role in the efficacy and/or toxicity of chemotherapy agents has been demonstrated, the impacts of pemetrexed on the gut microbiota and on gastrointestinal inflammation remain unknown. The objective of this study was to evaluate the impact of pemetrexed and the tumor graft on the gut microbiota composition in immunodeficient mice. The faecal microbiota composition was studied with metabarcoding before, 24-h and one week after treatment. The colon epithelial barrier integrity was evaluated by histological examination, intestinal permeability measurement, and selected cytokines quantification. The tumor graft induced some variations in the microbiota composition. Pemetrexed further increased the relative abundance of Enterobacteriaceae and 3 families from the Firmicutes phylum: Enterococcaceae, Lactobacillaceae and Streptococcaceae. Pemetrexed also significantly altered the epithelial barrier integrity, which was associated with early inflammation. This pilot study shows that the association of a lung tumor graft with pemetrexed causes an alteration in the microbiota composition. Such information increases our knowledge about the impact of chemotherapy on the microbiota, which could help to minimize side effects and improve therapeutic effectiveness in the future.

[**The Regimen of Computed Tomography Screening for Lung Cancer: Lessons Learned Over 25 Years From the International Early Lung Cancer Action Program**](#) J Thorac Imaging. 2020 Jun 5. doi: 10.1097/RTI.0000000000000538. Online ahead of print.Claudia I Henschke 1   2 , Rowena Yip 1 , Dorith Shaham 3 , Javier J Zulueta 4 , Samuel M Aguayo 2 , Anthony P Reeves 5 , Artit Jirapatnakul 1 , Ricardo Avila 6 , Drew Moghanaki 7 , David F Yankelevitz 1 , I-ELCAP Investigators

We learned many unanticipated and valuable lessons since we started planning our study of low-dose computed tomography (CT) screening for lung cancer in 1991. The publication of the baseline results of the Early Lung Cancer Action Project (ELCAP) in Lancet 1999 showed that CT screening could identify a high proportion of early, curable lung cancers. This stimulated large national screening studies to be quickly started. The ELCAP design, which provided evidence about screening in the context of a clinical program, was able to rapidly expand to a 12-institution study in New York State (NY-ELCAP) and to many international institutions (International-ELCAP), ultimately working with 82 institutions, all using the common I-ELCAP protocol. This expansion was possible because the investigators had developed the ELCAP Management System for screening, capturing data and CT images, and providing for quality assurance. This advanced registry and its rapid accumulation of data and images allowed continual assessment and updating of the regimen of screening as advances in knowledge and new technology emerged. For example, in the initial ELCAP study, introduction of helical CT scanners had allowed imaging of the entire lungs in a single breath, but the images were obtained in 10 mm increments resulting in about 30 images per person. Today, images are obtained in submillimeter slice thickness, resulting in around 700 images per person, which are viewed on high-resolution monitors. The regimen provides the imaging acquisition parameters, imaging interpretation, definition of positive result, and the recommendations for further workup, which now include identification of emphysema and coronary artery calcifications. Continual updating is critical to maximize the benefit of screening and to minimize potential harms. Insights were gained about the natural history of lung cancers, identification and management of nodule subtypes, increased understanding of nodule imaging and pathologic features, and measurement variability inherent in CT scanners. The registry also provides the foundation for assessment of new statistical techniques, including artificial intelligence, and integration of effective genomic and blood-based biomarkers, as they are developed.

[**Real World Outcomes in KRAS G12C Mutation Positive Non-Small Cell Lung Cancer**](#) Lung Cancer. 2020 Jun 26;146:310-317. doi: 10.1016/j.lungcan.2020.06.030. Online ahead of print. Wanyuan Cui 1 , Fanny Franchini 2 , Marliese Alexander 3 , Ann Officer 4 , Hui-Li Wong 5 , Maarten IJzerman 6 , Jayesh Desai 7 , Benjamin J Solomon 7

BACKGROUND: KRAS mutations are found in 20-30 % of non-small cell lung cancers (NSCLC) and were traditionally considered undruggable. KRASG12C mutation confers sensitivity to KRASG12C covalent inhibitors, however its prognostic impact remains unclear. This study assesses the frequency, clinical features, prevalence of brain metastases and outcomes in KRASG12C NSCLC in a real-world setting. **METHODS:** Patients enrolled in the prospective Thoracic Malignancies Cohort (TMC) between July 2012 to October 2019 with recurrent/metastatic non-squamous NSCLC, available KRAS results, and without EGFR/ALK/ROS1 gene aberrations, were selected. Data was extracted from TMC and patient records. Clinicopathologic features, treatment and overall survival (OS) was compared for KRAS wildtype (KRASWT) and KRAS mutated (KRASmut); and KRASG12C and other (KRASother) mutations. **RESULTS:** Of 1386 NSCLC patients, 1040 were excluded: non-metastatic/recurrent (526); unknown KRAS status (356); ALK/EGFR/ROS1 positive (154); duplicate (4). Of 346 patients analysed, 144 (42 %) were KRASmut, of whom 65 (45 %) were KRASG12C. All patients with KRASG12C were active or ex-smokers, compared to 92 % of KRASother and 83 % of KRASWT. The prevalence of brain

metastases during follow-up was similar between KRASmut and KRASWT (33 % vs 40 %, p = 0.17), and KRASG12C and KRASother (40 % vs 41 %, p = 0.74). The proportion of patients receiving one or multiple lines of systemic therapy was comparable. OS was similar between KRASmut and KRASWT (p = 0.54), and KRASG12C and KRASother (p = 0.39). **CONCLUSION:** Patients with KRASmut and KRASWT, and KRASG12C and KRASother NSCLC have comparable clinical features, treatment and survival. While not prognostic, KRASG12C may be an important predictive biomarker as promising KRASG12C covalent inhibitors continue to be developed.

[**Lung Cancer Screening Decisional Needs Among African American Smokers of Lower Socioeconomic Status**](#) Ethn Health. 2020 Jun 5;1-19. doi: 10.1080/13557858.2020.1771681. Online ahead of print. Randi M Williams 1 , Kenneth H Beck 2 , James Butler 3rd 2 , Sunmin Lee 3 , Min Qi Wang 2 , Kathryn L Taylor 1 , Cheryl L Knott 2
OBJECTIVES: Adherence to most evidence-based cancer screenings is lower among African Americans due to system- and individual-level factors that contribute to persistent disparities. Given the recommendation for low-dose computed tomography (LDCT) screening among individuals at high risk for lung cancer, we sought to describe aspects of decision-making for LDCT among African Americans and to examine associations between select components of decision-making and screening-related intentions. **DESIGN:** African Americans (N = 119) with a long-term smoking history, aged 55-80 years, and without lung cancer were recruited to participate in a cross-sectional survey. We measured knowledge, awareness, decisional conflict, preferences, and values related to lung cancer screening. **RESULTS:** The majority of the study population was of lower socioeconomic status (67.2% had an annual income of ≤$20,000) and long-term current (79%) smokers. Participants had a median 20 pack-years smoking history. Most participants (65.8%) had not heard of LDCT and the total lung cancer screening knowledge score was M = 7.1/15.0 (SD = 1.8). Participants with higher scores on the importance of the pros and cons of screening expressed greater likelihood of talking with a doctor, family, and friends about screening (p's < .10). **CONCLUSIONS:** Findings have implications for addressing the decisional needs of lower socioeconomic African American current and former smokers to promote informed decision-making for LDCT.

[**Effective Educational Approaches to Training Physicians About Lung Cancer Screening**](#) J Cancer Educ. 2020 Jun 5. doi: 10.1007/s13187-020-01784-4. Online ahead of print. Katherine Ortmeyer 1 , Grace X Ma 2 , Larry R Kaiser 3 , Cherie Erkmen 4
In 2013, the U.S. Preventative Services Task Force recommended low-dose computed tomography (LDCT) for lung cancer screening (LCS) after a national trial demonstrated a 20% reduction in lung cancer mortality with LDCT. Implementation of LCS employing LDCT depends heavily on physician education regarding multiple factors, including eligibility criteria, potential benefits and harms, and shared decision-making. To date, there are no studies of educational approaches for teaching physicians about LCS. This study aims to assess the feasibility and effectiveness of implementing an interactive, group-based learning (GBL) curriculum to teach physicians about LCS. A prospective study was conducted at two nearby institutions from 2017 to 2019 comparing GBL with a lecture format as measured by total knowledge about LCS, acceptability of the educational format, and ease of implementation. We surveyed participants regarding total knowledge and format acceptance. Results were compared to determine whether GBL is an effective and feasible educational strategy for LDCT and LCS education. Residents and faculty participating in GBL demonstrated greater total knowledge compared with residents and faculty participating in the lecture format. Participants in both cohorts preferred a mix of GBL and lecture formats. All participants believed that GBL facilitates implementation of LCS better than lecture-based learning. GBL is an effective and feasible approach for educating physicians about

LCS, though it is more time- and resource-intensive than a lecture approach. However, healthcare providers believe GBL will facilitate implementation of LCS more than lectures.

[A Review of the Role of MRI in Diagnosis and Treatment of Early Stage Lung Cancer](#) Clin Transl Radiat Oncol. 2020 Jun 6;24:16-22. doi: 10.1016/j.ctro.2020.06.002. eCollection 2020 Sep.
Austin J Sim 1 , Evangelia Kaza 2 , Lisa Singer 2 , Stephen A Rosenberg 1   3

Despite magnetic resonance imaging (MRI) being a mainstay in the oncologic care for many disease sites, it has not routinely been used in early lung cancer diagnosis, staging, and treatment. While MRI provides improved soft tissue contrast compared to computed tomography (CT), an advantage in multiple organs, the physical properties of the lungs and mediastinum create unique challenges for lung MRI. Although multi-detector CT remains the gold standard for lung imaging, advances in MRI technology have led to its increased clinical relevance in evaluating early stage lung cancer. Even though positron emission tomography is used more frequently in this context, functional MR imaging, including diffusion-weighted MRI and dynamic contrast-enhanced MRI, are emerging as useful modalities for both diagnosis and evaluation of treatment response for lung cancer. In parallel with these advances, the development of combined MRI and linear accelerator devices (MR-linacs), has spurred the integration of MRI into radiation treatment delivery in the form of MR-guided radiotherapy (MRgRT). Despite challenges for MRgRT in early stage lung cancer radiotherapy, early data utilizing MR-linacs shows potential for the treatment of early lung cancer. In both diagnosis and treatment, MRI is a promising modality for imaging early lung cancer.

[Using Implementation Science to Disseminate a Lung Cancer Screening Education Intervention Through Community Health Workers](#) J Community Health. 2020 Jun 27. doi: 10.1007/s10900-020-00864-2. Online ahead of print. Lovoria B Williams 1 , Brent J Shelton 2 , Maria L Gomez 3 , Yazan D Al-Mrayat 3 , Jamie L Studts 4

National lung cancer screening with low dose computed tomography (LDCT) uptake is suboptimal. One factor contributing to slow uptake is lack of awareness. Trained Community Health Workers (CHWs) may be effective in increasing lung cancer screening awareness among disparate populations, however little is known about the processes necessary to scale an intervention for implementation by CHWs in a new area. We examined implementation processes with the RE-AIM framework and pilot tested a CHW-delivered lung cancer education intervention based on the Health Belief Model. We measured pre-post participant knowledge, attitudes and beliefs regarding cancer screening, lung cancer stigma, and intent to obtain LDCT screening. We used community-engaged strategies to collaborate with a local health system, to identify CHWs. CHWs were trained to recruit participants and deliver the one-session lung cancer education intervention. Seven CHWs and eight community sites participated. Participants (n = 77) were female (53%) primarily low income (62.9%); tobacco use was high (36.9%). Post intervention changes in lung cancer screening knowledge (p = < .0001), attitudes regarding lung cancer screening benefit (p = .034) and lung cancer stigma. (p = .024) We learned important lessons that will be useful in subsequent scaling. Collaborating with a local health system is a promising method to disseminate a lung cancer screening education intervention.

[Adaptation and Preliminary Evaluation of a Lung Cancer Screening Decision Tool for Older Chinese American Populations](#) J Natl Med Assoc. 2020 Jun 27;S0027-9684(20)30114-0. doi: 10.1016/j.jnma.2020.05.016. Online ahead of print. Chien-Ching Li 1 , Alicia K Matthews 2 , Tingqing Wu 3

BACKGROUND: Lung cancer is a significant health issue among Chinese Americans. The study purpose was to translate and culturally adapt the Agency for Healthcare Research and Quality's (AHRQ) lung cancer screening decision tool to the needs of older Chinese American smokers. **METHODS:** This

study used a mixed methods approach. In the first phase, AHRQ lung cancer screening decision aid was translated from English to Chinese. The second phase consisted of a paper and pencil survey (N = 50) designed to measure knowledge and attitudes regarding lung screening. Finally, focus groups (N = 5, 27 participants) were conducted to obtain input on the translated and culturally adapted AHRQ lung cancer screening DA. **RESULTS:** The mean age of participants was 70.4 years (SD = 5.4) and the majority were male (n = 42; 84%). Seventy-four percent of the sample reported being a former smoker and 26% a current smoker. Perceived risk for lung cancer was low (26%) and the majority of participants (70%) were unaware of lung cancer screening. Perceived benefits (e.g., early cancer detection) and barriers of LDCT screening (e.g., costs) were reported by participants. The qualitative findings were largely consistent with the quantitative results. Following the revisions to the translated AHRQ DA, participants reported satisfaction with the readability and information provided. **CONCLUSIONS:** Lung cancer screening represents an evidence-based approach for reducing lung cancer morbidity and mortality among chronic high frequency smokers. Culturally targeting evidence-based lung cancer screening decision-aids to the language, cultural and health literacy needs of high risk populations may increase uptake of lung cancer early detection screening.

[Practice, Clinician, and Patient Factors Associated With the Adoption of Lung Cancer Screening](#)

Camille J Hochheimer 1 , Roy T Sabo 2 3 , Sebastian T Tong 3 , Matthew Westfall 3 , Susan E Wolver 4 , Stacie Carney 5 , Teresa Day 3 , Alex H Krist 3 6

OBJECTIVES: Lung cancer remains the leading cause of cancer-related deaths in the United States. In 2013, the US Preventive Services Task Force recommended annual screening for lung cancer with low-dose computed tomography in adults meeting certain criteria. This study seeks to assess lung cancer screening uptake in three health systems. **SETTING:** This study was part of a randomized controlled trial to engage underserved populations in preventive care and includes 45 primary care practices in eight states. **METHODS:** Practice and clinician characteristics were manually collected. Lung cancer was measured from electronic health record data. A generalized linear mixed model was used to assess characteristics associated with screening. **RESULTS:** Patient records between 2012 and 2016 were examined. Lung cancer screening uptake overall increased only slightly after the guideline change (2.8-5.6%, p < 0.01). One health system did not show an increase in uptake (0.2-0.1%, p = 0.32), another had a clinically insignificant increase (1.5-2.9%, p < 0.01), and the third nearly doubled its higher baseline screening rate (10.4-19.1%, p < 0.01). Within the third health system, patients more likely to be screened were older, male, had more comorbid conditions, visited the office more frequently, were seen in practices closer to the screening clinic, or were uninsured or covered by Medicare or Medicaid. **CONCLUSIONS:** Certain patients appeared more likely to be screened. The only health system with increased lung cancer screening explicitly promoted screening rather than relying on clinicians to implement the new guideline. Systems approaches may help increase the low uptake of lung cancer screening.

[Reexamining Rates of Decline in Lung Cancer Risk After Smoking Cessation: A Meta-Analysis](#)

Marissa Reitsma 1 , Parkes Kendrick 1 , Jason Anderson 1 , Nicholas Arian 1 , Rachel Feldman 1 , Emmanuela Gakidou 1 , Vin Gupta 1 2

RATIONALE: Prior studies have questioned whether prevailing eligibility criteria for lung cancer screening are sufficiently inclusive of former smokers who remain at elevated risk of disease outside current screening windows. **OBJECTIVE:** Characterize the percent of the reducible relative risk remaining (RRR) for lung cancer as a function of years since quitting. **METHODS:** MEDLINE and PubMed were searched from January 2011 to May 2018; key search terms included smoking and cancer.

Current smoker relative risks were extracted to represent former smokers at zero years since quitting; data were transformed assuming a lognormal distribution. **RESULTS:** The main review included 49 prospective cohorts across 18 studies comprising a total of 139 RRs from 20 countries and territories. At one year since quitting, the percentage of RRR for lung cancer was 81.4% [64.1-98.2]. At five years since quitting, RRR was 57.2% [45.7-67.3]; at 10 years: 36.9% [28.3-47.9]; at 15 years, 26.7% [20.2-34.3]; at 20 years, 19.7% [13.3-26.4]. If eligibility criteria in the US were broadened to screen former smokers up to 20 years since quitting, we estimate an additional 4.2 [3.9-4.5] million former smokers between 55-80 years of age would be eligible for lung cancer screening. **CONCLUSION:** At the critical screening threshold of 15 years since quitting, the percentage of excess risk for lung cancer remains high and only marginally declines at time points afterward, excluding millions of former smokers who remain at elevated risk of malignancy. A risk-based screening algorithm for lung cancer screening that de-emphasizes time post-cessation as a key screening determinant would more likely capture these former smokers who remain at elevated risk of malignancy.

[**Multi-model Ensemble Learning Architecture Based on 3D CNN for Lung Nodule Malignancy Suspiciousness Classification**](#) J Digit Imaging. 2020 Jun 30. doi: 10.1007/s10278-020-00372-8. Online ahead of print. Hong Liu 1 , Haichao Cao 1 , Enmin Song 2 , Guangzhi Ma 1 , Xiangyang Xu 1 , Renchao Jin 1 , Chuhua Liu 1 , Chih-Cheng Hung 3
Classification of benign and malignant in lung nodules using chest CT images is a key step in the diagnosis of early-stage lung cancer, as well as an effective way to improve the patients' survival rate. However, due to the diversity of lung nodules and the visual similarity of lung nodules to their surrounding tissues, it is difficult to construct a robust classification model with conventional deep learning-based diagnostic methods. To address this problem, we propose a multi-model ensemble learning architecture based on 3D convolutional neural network (MMEL-3DCNN). This approach incorporates three key ideas: (1) Constructed multi-model network architecture can be well adapted to the heterogeneity of lung nodules. (2) The input that concatenated of the intensity image corresponding to the nodule mask, the original image, and the enhanced image corresponding to which can help training model to extract advanced feature with more discriminative capacity. (3) Select the corresponding model to different nodule size dynamically for prediction, which can improve the generalization ability of the model effectively. In addition, ensemble learning is applied in this paper to further improve the robustness of the nodule classification model. The proposed method has been experimentally verified on the public dataset, LIDC-IDRI. The experimental results show that the proposed MMEL-3DCNN architecture can obtain satisfactory classification results.

[**Molecular Matching and Treatment Strategies for Advanced Stage Lung Cancer at Dartmouth-Hitchcock Medical Center: A Three-Year Review of a Molecular Tumor Board**](#) Pract Lab Med. 2020 Jun 12;21:e00174. doi: 10.1016/j.plabm.2020.e00174. eCollection 2020 Aug. Erica B Bernhardt 1 , Mary D Chamberlin 2 , Ivan P Gorlov 3 , et al.
Matching of actionable tumor mutations with targeted therapy increases response rates and prolongs survival in lung cancer patients. Drug development and trials targeting genetic alterations are expanding rapidly. We describe the role of a Molecular Tumor Board (MTB) in the design of molecularly informed treatment strategies in our lung cancer patient population. Tumor DNA was sequenced using a 50-gene targeted next-generation sequencing panel. Cases were evaluated by a multidisciplinary MTB who suggested a course of treatment based on each patient's molecular findings. During a three-year period, 21 lung cancer patients were presented at the MTB. All patients lacked common activating EGFR mutations and ALK rearrangements. One patient had Stage IIIb disease; all others were Stage IV; 18 patients had received ≥1 prior line of therapy (range 0-5). Suggestions for treatment with a targeted therapy were made for 19/21 (90.5%) patients, and four patients (21%) underwent treatment with a targeted agent, two as part

of a clinical trial. Identified barriers to treatment with targeted therapy included: ineligibility for clinical trials (n = 2), lack of interest in study/distance to travel (n = 2), lack of disease progression (n = 2), poor performance status (n = 5), decision to treat next with immunotherapy (n = 3), and unknown (n = 1). For the majority of lung cancer patients, the MTB provided recommendations based on tumor genetic profiles. Identified barriers to treatment suggest that presentation to the MTB at earlier stages of disease may increase the number of patients eligible for treatment with a genetically informed targeted agent.

[Peritumoral and Intratumoral Radiomic Features Predict Survival Outcomes Among Patients Diagnosed in Lung Cancer Screening](#) Sci Rep. 2020 Jun 29;10(1):10528. doi: 10.1038/s41598-020-67378-8. Jaileene Pérez-Morales 1 , Ilke Tunali 2 3 , Olya Stringfield 2 , et al.

The National Lung Screening Trial (NLST) demonstrated that screening with low-dose computed tomography (LDCT) is associated with a 20% reduction in lung cancer mortality. One potential limitation of LDCT screening is overdiagnosis of slow growing and indolent cancers. In this study, peritumoral and intratumoral radiomics was used to identify a vulnerable subset of lung patients associated with poor survival outcomes. Incident lung cancer patients from the NLST were split into training and test cohorts and an external cohort of non-screen detected adenocarcinomas was used for further validation. After removing redundant and non-reproducible radiomics features, backward elimination analyses identified a single model which was subjected to Classification and Regression Tree to stratify patients into three risk-groups based on two radiomics features (NGTDM Busyness and Statistical Root Mean Square [RMS]). The final model was validated in the test cohort and the cohort of non-screen detected adenocarcinomas. Using a radio-genomics dataset, Statistical RMS was significantly associated with FOXF2 gene by both correlation and two-group analyses. Our rigorous approach generated a novel radiomics model that identified a vulnerable high-risk group of early stage patients associated with poor outcomes. These patients may require aggressive follow-up and/or adjuvant therapy to mitigate their poor outcomes.

[Implementing Lung Cancer Screening and Prevention in Academic Centers, Affiliated Network Offices and Collaborating Care Sites](#) J Clin Med. 2020 Jun 11;9(6):E1820. doi: 10.3390/jcm9061820. Cary A Presant 1 2 , Ravi Salgia 1 2 , Prakash Kulkarni 1 2 , et al.

Lung cancer is one of the deadliest and yet largely preventable neoplasms. Smoking cessation and lung cancer screening are effective yet underutilized lung cancer interventions. City of Hope Medical Center, a National Cancer Institute (NCI)- designated comprehensive cancer center, has 27 community cancer centers and has prioritized tobacco control and lung cancer screening throughout its network. Despite challenges, we are implementing and monitoring the City of Hope Tobacco Control Initiative including 1) a Planning and Implementation Committee; 2) integration of IT, e.g., medical records and clinician notification/prompts to facilitate screening, cessation referral, and digital health, e.g., telehealth and social media; 3) clinician training and endorsing national guidelines; 4) providing clinical champions at all sites for site leadership; 5) Coverage and Payment reform and aids to facilitate patient access and reduce cost barriers; 6) increasing tobacco exposure screening for all patients; 7) smoking cessation intervention and evaluation-patient-centered recommendations for smoking cessation for all current and recent quitters along with including QuitLine referral for current smokers and smoking care-givers; and 8) establishing a Tobacco Registry for advancing science and discoveries including team science

[Utilization of Lung Cancer Screening in the Medicare Fee-for-Service Population](#)
Chest. 2020 Jun 17;S0012-3692(20)31674-3. doi: 10.1016/j.chest.2020.05.592. Online ahead of print. Tina D Tailor 1 , Betty C Tong 2 , Junheng Gao 3 , Louise M Henderson 4 , Kingshuk Roy Choudhury 5 , Geoffrey D Rubin 6

BACKGROUND: A number of organizations, including the U.S. Preventative Services Task Force (USPSTF), recommend lung cancer screening (LCS) with low dose computed tomography (LDCT) for

high-risk current and former smokers. In 2015, Medicare issued a decision to cover LCS as a preventative health benefit, however utilization in the Medicare population has not been thoroughly examined. **RESEARCH QUESTION:** Our objective was to evaluate the early utilization of LCS in the Medicare fee-for-service (FFS) population and determine the relationship(s) among beneficiary sociodemographic characteristics, geographical location, and utilization. **STUDY DESIGN:** and Methods.This cross-sectional observational study utilized 100% Medicare FFS claims files for Medicare beneficiaries receiving LCS between January 1, 2016 - December 31, 2016. We estimated the LCS eligible Medicare population using population and smoking data from the U.S. Census Bureau and Centers for Disease Control and Prevention (CDC). We assessed variation in LCS rates by beneficiary characteristics and geography using univariate and multivariate regression, the latter also including how interactions between geographical location and race/ethnicity influence screening. **RESULTS:** A total of 103,892 Medicare FFS beneficiaries received LCS in 2016, comprising 4.1% (95% CI 3.9 - 4.3%) of the estimated LCS eligible Medicare population. Accounting for the interactions between race/ethnicity and U.S. region, non-White (Black, Hispanic) beneficiaries in all U.S. regions were screened with less frequency than White beneficiaries (p<0.001). Screening rates in the Northeast were significantly higher than other regions (adjusted rate ratio (95% CI) of Northeast relative to South: 1.83 (1.36-2.46)). **INTERPRETATION:** The early adoption of LCS amongst Medicare beneficiaries was low. Our results suggest geographic and racial disparities in screening utilization, with populations in the South and those of non-White race/ethnicity being screened with less frequency. Further work is needed to improve LCS uptake and ensure consistent use by all at-risk populations.

Standardized Reporting and Management of Suspicious Findings on Chest Computed Tomography Is Associated With Improved Lung Cancer Diagnosis in an Observational Study

Thomas H Urbania 1 , Jennifer R Dusendang 2 , Lisa J Herrinton 3 , Stacey Alexeeff 2 , Douglas A Corley 2 , Sora Ely 4 , Ashish Patel 4 , Todd Osinski 1 , Lori C Sakoda 2

BACKGROUND: Follow-up of chest computed tomography (CT) findings suspicious for lung cancer may be delayed because of inadequate documentation. Standardized reporting and follow-up may reduce time to diagnosis and care for lung cancer. **STUDY DESIGN AND METHODS:** We implemented a reporting system that standardizes tagging of chest CT reports by classifying pulmonary findings. The system also automates referral of patients with findings suspicious for lung cancer to a multidisciplinary care team for rapid review and follow-up. The system was designed to reduce the time to diagnosis, particularly for early-stage lung cancer. We evaluated the effectiveness of this system using a quasi-experimental stepped wedge cluster design, examining 99,148 patients who underwent diagnostic (non-screening) chest CT from 2015 to 2017 who had not had a chest CT in the preceding 24 months. We evaluated the association of the intervention with incidence of diagnosis and surgical treatment of early-stage (I, II) and late-stage (III, IV) lung cancer within 120 days after chest CT. **RESULTS:** 40% of patients received the intervention. Among 2,856 (2.9%) patients who were diagnosed with lung cancer, 28% had early-stage disease. In multivariable analyses, the intervention was associated with a 24% greater odds of early-stage diagnosis (OR = 1.24, 95% CI, 1.09-1.41) and no change in the odds of late-stage diagnosis (OR=1.04, 95% CI, 0.95-1.14). The intervention was not associated with the rate of surgical treatment within 120 days. **INTERPRETATION:** In this large quasi-experimental community-based observational study, implementation of a system that combines standardized tagging of chest CT reports with clinical navigation was effective for increasing the diagnosis of early-stage lung cancer.

CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES

Salvage Stereotactic Body Radiation Therapy for Isolated Local Recurrence After Primary Surgical Resection of Non-small-cell Lung Cancer Clin Lung Cancer. 2020 Jun 2;S1525-7304(20)30165-0. doi: 10.1016/j.cllc.2020.05.025. Online ahead of print. Sarah M C Sittenfeld 1 , Aditya Juloori 2 , Chandana A Reddy 1 , Kevin L Stephans 1 , Gregory M M Videtic 3

INTRODUCTION: We sought to evaluate the safety and efficacy of stereotactic body radiation therapy (SBRT) as salvage treatment for local recurrence after prior surgical resection for non-small-cell lung cancer (NSCLC). **MATERIALS AND METHODS:** We surveyed our prospective lung SBRT registry for patients who received salvage SBRT (sSBRT) for local recurrence after previous resection of a primary NSCLC. Following sSBRT, local control, distant metastases, overall survival, and treatment-related toxicity were evaluated. **RESULTS:** From 2004 to 2017, 48 patients met inclusion criteria. At initial surgery, 44 (83%) patients had stage I to II disease, and surgical approaches were 47.9% wedge resection, 4.2% segmentectomy, 43.8% lobectomy, and 4.2% bilobectomy. The median time to local recurrence after surgery was 26.4 months, and 36 (75%) recurrences were biopsy-proven. Surgical salvage was not possible owing to un-resectability or underlying comorbidities in 45 (93.8%) patients. Most (68.8%) patients received 50 Gy in 5 fractions. The median follow-up after sSBRT was 22.6 months (range, 3.8-108.8 months). Eight (16.7%) patients experienced local or lobar failure, and 9 (19.1%) patients had nodal failure at a median of 12.5 months (range, 2-66.1 months). Nineteen (39.6%) patients failed distantly at a median of 11.4 months. The median overall survival after sSBRT was 29.3 months. A total of 72.9% of patients experienced no toxicity after sSBRT. Three (6.3%) patients developed grade III toxicity (cough, atelectasis, or soft tissue necrosis) following sSBRT. **CONCLUSIONS:** Similar to SBRT for primary early stage NSCLC, sSBRT for local relapse following surgical resection of NSCLC offers high rates of local control with limited toxicity. Distant failure remains the primary pattern of failure.

Peripheral Cytokines Are Not Influenced by the Type of Surgical Approach for Non-Small Cell Lung Cancer by Four Weeks Postoperatively Lung Cancer. 2020 Jun 27;146:303-309. doi: 10.1016/j.lungcan.2020.06.022. Online ahead of print. Erin M Corsini 1 , Qi Wang 2 , Hai T Tran 3 , et al.

OBJECTIVES: The influence of surgical approach on systemic inflammatory response and the subsequent oncologic impact for non-small cell lung cancer is debated. We aimed to measure the effects of thoracic surgical approach on peripheral cytokine milieu over time. **METHODS:** Patients undergoing primary lung resection without neoadjuvant therapy (2016-2018) were evaluated. A panel of 43 cytokines, angiogenic factors, and inflammatory molecules (CAFs) were evaluated in peripheral blood preoperatively, at 24 -hs and 4-weeks postoperatively. Differences between CAFs in patients undergoing thoracotomy versus video-assisted thoracoscopic surgery (VATS) at all timepoints were assessed using Student's t-test. **RESULTS:** 76 patients with available peripheral CAF panels met inclusion criteria. Thoracotomy was performed in 53 (70 %) patients while VATS was undertaken in 23 (30 %). Upon examination of known inflammatory CAFs, including IL-1β, IL-6, IL-8, IL-10, IFN-γ, and soluble (s) CD27, no differences were detected at 24 h or 4 weeks postoperatively between surgical groups. Examination of trends over time did not demonstrate any temporal derangements for these CAFs, with return to baseline levels by 4 weeks postoperatively for both groups. Evaluation of soluble (s) checkpoint molecules, including sPD-1, sPD-L1, sTIM-3, and sCTLA-4, did not reveal any differences in the immediate postoperative or long-term recovery period. **CONCLUSIONS:** Peripheral immune profiles following pulmonary resection do not appear to differ between VATS and thoracotomy postoperatively. CAF fluctuations are transient and recover rapidly. These results, at the peripheral cytokine level, suggest that the surgical approach for lung cancer is unlikely to alter the effectiveness of novel immune-modulating systemic therapies, although more studies are needed to validate these findings.

[Clinical Impacts of EGFR Mutation Status: Analysis of 5,780 Surgically Resected Lung Cancer Cases](#) Ann Thorac Surg. 2020 Jun 29;S0003-4975(20)30982-6. doi: 10.1016/j.athoracsur.2020.05.041. Online ahead of print. Kenichi Suda 1 , Tetsuya Mitsudomi 2 , Yasushi Shintani 3 , et al.
BACKGROUND: To elucidate the clinical, pathologic, and prognostic impacts of EGFR mutation and mutation subtypes in early-stage lung cancer, we conducted a retrospective analysis of the Japanese Joint Committee of Lung Cancer Registry database (a nationwide database for surgically-resected lung cancer patients; n = 18,973). **METHODS:** Of 13,951 patients classified as non-squamous non-small cell lung cancer in the database, 5,780 patients (41.0%) had been tested for EGFR mutation and were included in this study. **RESULTS:** EGFR mutation was detected in 2,410 patients (41.7%), and presence of EGFR mutation was significantly correlated with clinicopathological factors such as the presence of ground-glass opacity (P < 0.001) and better prognosis. Analysis of initial recurrence sites identified significantly higher frequencies of brain and adrenal gland metastases in patients with and without EGFR mutation, respectively. Of 2,410 patients with EGFR mutations, 983 (40.8%) had exon 19 deletion (Exon 19 Del), 1,170 (48.5%) had L858R mutation, and 257 (10.7%) had other EGFR mutations. Higher smoking rate was found in patients with other EGFR mutations (p = 0.02). In the comparison of Exon 19 Del and L858R, we found that Exon 19 Del correlated with younger age (P < 0.001), higher rate of pure solid tumors (P < 0.001), advanced pathological stage (trend P = 0.0004), and poorer recurrence-free survival (P = 0.001). **CONCLUSIONS:** In addition to clinicopathological and prognostic impacts of EGFR mutation status, tumors with Exon 19 Del have a more aggressive phenotype and poorer prognosis than those with L858R in early-stage lung cancers.

[Standardized Reporting and Management of Suspicious Findings on Chest Computed Tomography Is Associated With Improved Lung Cancer Diagnosis in an Observational Study](#) Chest. 2020 Jun 17;S0012-3692(20)31677-9. doi: 10.1016/j.chest.2020.05.595. Online ahead of print.
BACKGROUND: Follow-up of chest computed tomography (CT) findings suspicious for lung cancer may be delayed because of inadequate documentation. Standardized reporting and follow-up may reduce time to diagnosis and care for lung cancer. **STUDY DESIGN AND METHODS:** We implemented a reporting system that standardizes tagging of chest CT reports by classifying pulmonary findings. The system also automates referral of patients with findings suspicious for lung cancer to a multidisciplinary care team for rapid review and follow-up. The system was designed to reduce the time to diagnosis, particularly for early-stage lung cancer. We evaluated the effectiveness of this system using a quasi-experimental stepped wedge cluster design, examining 99,148 patients who underwent diagnostic (non-screening) chest CT from 2015 to 2017 who had not had a chest CT in the preceding 24 months. We evaluated the association of the intervention with incidence of diagnosis and surgical treatment of early-stage (I, II) and late-stage (III, IV) lung cancer within 120 days after chest CT. **RESULTS:** 40% of patients received the intervention. Among 2,856 (2.9%) patients who were diagnosed with lung cancer, 28% had early-stage disease. In multivariable analyses, the intervention was associated with a 24% greater odds of early-stage diagnosis (OR = 1.24, 95% CI, 1.09-1.41) and no change in the odds of late-stage diagnosis (OR=1.04, 95% CI, 0.95-1.14). The intervention was not associated with the rate of surgical treatment within 120 days. **INTERPRETATION:** In this large quasi-experimental community-based observational study, implementation of a system that combines standardized tagging of chest CT reports with clinical navigation was effective for increasing the diagnosis of early-stage lung cancer.

[Alternatives to Surgery for Early-Stage Non-Small Cell Lung Cancer: Thermal Ablation](#) Clin Chest Med. 2020 Jun;41(2):197-210. doi: 10.1016/j.ccm.2020.02.002.Matthew T Quirk 1 , Shimwoo Lee 2 , Nikitha Murali 3 , Scott Genshaft 2 , Fereidoun Abtin 2 , Robert Suh 2

Thermal ablation involves the application of heat or cold energy to the lung under image guidance to eradicate tumors. It is indicated for treatment of early-stage non-small cell lung cancer in nonsurgical patients. Ablation technologies have advanced, such that nearly all small tumors can now be treated safely and effectively. Ablation does not cause a lasting decline in pulmonary function tests and may therefore be used to treat multiple synchronous and metachronous lung tumors, a chief advantage over other treatments. Large series with intermediate- and long-term data have been reported showing favorable overall survival, similar to radiation therapy.

NSCLC – Systemic Therapies (Chemotherapy, Targeted Therapy, and Immunotherapy)

A Randomised Open-Label Phase III Trial Evaluating the Addition of Denosumab to Standard First-Line Treatment in Advanced NSCLC - The ETOP and EORTC SPLENDOUR Trial

J Thorac Oncol. 2020 Jun 18;S1556-0864(20)30481-0. doi: 10.1016/j.jtho.2020.06.011. Online ahead of print. Solange Peters 1 , Sarah Danson 2 , Baktiar Hasan 3 , et al.

INTRODUCTION: RANKL stimulates NF-kB-dependent cell-signalling and acts as the primary signal for bone resorption. Retrospective analysis of a large trial comparing denosumab versus zoledronic acid in bone metastatic solid tumours suggested significant overall survival (OS) advantage for lung cancer patients with denosumab. The randomised open-label phase III SPLENDOUR trial was designed to evaluate whether the addition of denosumab to standard first-line platinum-based doublet chemotherapy improves OS in advanced NSCLC. **METHODS:** Stage IV NSCLC patients were randomised 1:1 to either chemotherapy with or without denosumab (120mg every 3-4 weeks), stratified by presence of bone metastases (at diagnosis), ECOG performance status, histology and region. To detect an OS increase from 9-11.25 months (HR=0.80), 847 OS events were required. The trial closed prematurely due to decreasing accrual rate. **RESULTS:** 514 patients were randomised, 509 receiving ≥1 dose of assigned treatment (chemotherapy:252, chemotherapy-denosumab:257). Median age was 66.1 years, 71% male, 59% former smokers. Bone metastases were identified in 275(53%) patients. Median OS(95%CI) was 8.7(7.6-11.0) in the control versus 8.2(7.5-10.4) months in the chemotherapy-denosumab-arm, (HR=0.96;95%CI:[0.78-1.19]; 1-sided P=0.36). For patients with bone metastasis HR=1.02(95%CI:[0.77-1.35]), while for those without HR=0.90(95%CI:[0.66-1.23]). Grade≥3 adverse events were observed in 40.9%/5.2%/8.7% versus 45.5%/10.9%/10.5% of patients. Conditional power for OS benefit was ≤10%. **CONCLUSIONS:** Denosumab was well tolerated without unexpected safety concerns. There was no OS improvement for denosumab when added to chemotherapy in the ITT, and in the subgroups with and without bone metastases. Our data do not provide evidence of a clinical benefit for denosumab in NSCLC patients without bone metastases.

Circulating miRNAs and Extracellular Vesicle Containing miRNAs as Response Biomarkers of Anti PD-1/PD-L1 Therapy in Non-Small-Cell Lung Cancer

J Thorac Oncol. 2020 Jun 18;S1556-0864(20)30467-6. doi: 10.1016/j.jtho.2020.05.022. Online ahead of print. Takehito Shukuya 1 , Vikas Ghai 2 , Joseph M Amann 3 , Tamio Okimoto 1 , Konstantin Shilo 4 , Taek-Kyun Kim 2 , Kai Wang 2 , David P Carbone 5

BACKGROUND: Anti PD-1/PD-L1 antibody therapy is a standard treatment for advanced non-small cell lung cancer (NSCLC), and PD-L1 immunohistochemistry is used as a predictive biomarker for therapeutic response. However, because not all NSCLC patients with a high PD-L1 respond, and some patients with low PD-L1 expression show durable benefit, more accurate, predictive biomarkers are needed. Circulating miRNA and miRNA packaged in extracellular vesicles (EVs) are considered to play a role in intercellular communication among immune cells and between immune cells and tumor cells and may represent a good source of mechanism-related biomarkers. **METHODS**: Pretreatment plasma of advanced NSCLC patients treated with single agent anti PD-1 or PD-L1 antibody was used in this study.

Plasma EVs were isolated using size-exclusion chromatography. Whole plasma and EV containing RNAs were extracted. The miRNA profile was analyzed with a next generation sequencing platform.
RESULTS: Samples from 14 responders (patients who showed PR or SD ≥ 6 months) and 15 non-responders (patients who showed PD in RECIST) were analyzed. In total, 32 miRNAs (p=0.0030 - 0.0495) from whole plasma and 7 EV-associated miRNAs (p=0.041 - 0.0457) showed significant concentration differences between responders and non-responders. The results of some of these circulating miRNAs were validated in a separated cohort with 8 responders and 13 non-responders. The tumor PD-L1 level was also assessed using immunohistochemistry for patients involved in both cohorts.
CONCLUSIONS: Specific circulating miRNAs in whole plasma and plasma EVs are differentially expressed between responders and non-responders and have potential as predictive biomarkers for anti PD-1/PD-L1 treatment response.

[A Randomised Open-Label Phase III Trial Evaluating the Addition of Denosumab to Standard First-Line Treatment in Advanced NSCLC - The ETOP and EORTC SPLENDOUR Trial](#)

Solange Peters 1 , Sarah Danson 2 , Baktiar Hasan 3 , et al.
INTRODUCTION: RANKL stimulates NF-kB-dependent cell-signalling and acts as the primary signal for bone resorption. Retrospective analysis of a large trial comparing denosumab versus zoledronic acid in bone metastatic solid tumours suggested significant overall survival (OS) advantage for lung cancer patients with denosumab. The randomised open-label phase III SPLENDOUR trial was designed to evaluate whether the addition of denosumab to standard first-line platinum-based doublet chemotherapy improves OS in advanced NSCLC. **METHODS:** Stage IV NSCLC patients were randomised 1:1 to either chemotherapy with or without denosumab (120mg every 3-4 weeks), stratified by presence of bone metastases (at diagnosis), ECOG performance status, histology and region. To detect an OS increase from 9-11.25 months (HR=0.80), 847 OS events were required. The trial closed prematurely due to decreasing accrual rate. **RESULTS:** 514 patients were randomised, 509 receiving ≥1 dose of assigned treatment (chemotherapy:252, chemotherapy-denosumab:257). Median age was 66.1 years, 71% male, 59% former smokers. Bone metastases were identified in 275(53%) patients. Median OS(95%CI) was 8.7(7.6-11.0) in the control versus 8.2(7.5-10.4) months in the chemotherapy-denosumab-arm, (HR=0.96;95%CI:[0.78-1.19]; 1-sided P=0.36). For patients with bone metastasis HR=1.02(95%CI:[0.77-1.35]), while for those without HR=0.90(95%CI:[0.66-1.23]). Grade≥3 adverse events were observed in 40.9%/5.2%/8.7% versus 45.5%/10.9%/10.5% of patients. Conditional power for OS benefit was ≤10%. **CONCLUSIONS:** Denosumab was well tolerated without unexpected safety concerns. There was no OS improvement for denosumab when added to chemotherapy in the ITT, and in the subgroups with and without bone metastases. Our data do not provide evidence of a clinical benefit for denosumab in NSCLC patients without bone metastases.

[Association of Programmed Cell Death Ligand 1 Expression Status With Receipt of Immune Checkpoint Inhibitors in Patients With Advanced Non-Small Cell Lung Cancer](#)

Michael S Leapman 1 2 , Carolyn J Presley 3 , Weiwei Zhu 1 2 , Pamela R Soulos 1 2 , Kerin B Adelson 1 2 , Rebecca A Miksad, Daniel J Boffa 1 2 , Cary P Gross 1 2
IMPORTANCE: Initial approval for immune checkpoint inhibitors (ICIs) for treatment of advanced non-small cell lung cancer (NSCLC) was limited to patients with high levels of programmed cell death ligand 1 (PD-L1) expression. However, in the period after approval, it is not known how new evidence supporting efficacy of these treatments in patients with low or negative PD-L1 expression was incorporated into real-world practice. **OBJECTIVE:** To evaluate the association between PD-L1 testing and first-line ICI use. **DESIGN, SETTING, AND PARTICIPANTS:** This retrospective cohort study

(January 1, 2011, to December 31, 2018) used a deidentified nationwide electronic health record-derived database reflecting real-world care at more than 280 US community and academic cancer clinics (approximately 800 sites of care). Patients included those with advanced NSCLC without other identifiable variations diagnosed in the period after the US Food and Drug Administration's initial first-line approval of ICIs for patients with high PD-L1 expression (≥50%). **EXPOSURE**: First-line ICI treatment. **MAIN OUTCOMES AND MEASURES:** Patterns of PD-L1 testing and first-line ICI treatment among all patients and patients stratified by tumor histologic type (squamous vs nonsquamous). **RESULTS:** A total of 45 631 patients (mean [SD] age, 68.4 [9.6] years; 21 614 [47.4%] female) with advanced NSCLC were included in the study. PD-L1 testing increased from 468 (7.2%) in 2015 to 4202 (73.2%) in 2018. Within a subset of 7785 patients receiving first-line treatment in the period after first-line approval of pembrolizumab, those who received PD-L1 testing had a greater odds of receiving an ICI (odds ratio, 2.11; 95% CI, 1.89-2.36). Among patients with high PD-L1 expression (≥50%), 1541 (83.5%) received first-line ICI treatment; 776 patients (40.3%) with low PD-L1 expression (1%-49%) and 348 (32.3%) with negative PD-L1 expression (0%) also received ICIs. In addition, 755 untested patients (32.8%) were treated with a first-line ICI. The proportion of patients who received ICIs without PD-L1 testing increased during the study period (59 [17%] in quarter 4 of 2016 to 141 [53.8%] in quarter 4 of 2018). **CONCLUSIONS AND RELEVANCE:** In this study, use of first-line ICI treatment increased among patients with advanced NSCLC with negative, low, or untested PD-L1 expression status in 2016 through 2018. These findings suggest that national practice was rapidly responsive to new clinical evidence rather than adhering to regulatory guidance in place at the time.

[Chronic Immune Checkpoint Inhibitor Pneumonitis](#) J Immunother Cancer. 2020 Jun;8(1):e000840. doi: 10.1136/jitc-2020-000840.Jarushka Naidoo 1 2 , Tricia R Cottrell 3 , Evan J Lipson 4 2 , et al. **BACKGROUND:** Pneumonitis from immune checkpoint inhibitors (ICI) is a potentially fatal immune-related adverse event (irAE) from antiprogrammed death 1/programmed death ligand 1 immunotherapy. Most cases of ICI pneumonitis improve or resolve with 4-6 weeks of corticosteroid therapy. Herein, we report the incidence, clinicopathological features and management of patients with non-small cell lung cancer (NSCLC) and melanoma who developed chronic ICI pneumonitis that warrants ≥12 weeks of immunosuppression. **METHODS:** Patients with ICI pneumonitis were identified from institutional databases of ICI-treated patients with advanced melanoma and NSCLC between January 2011 and July 2018. ICI pneumonitis was defined as clinical/radiographic evidence of lung inflammation without alternative diagnoses, adjudicated by a multidisciplinary team. Chronic ICI pneumonitis was defined as pneumonitis that persists or worsens with steroid tapering, and necessitates ≥12 weeks of immunosuppression, after ICI discontinuation. Serial chest CT was used to assess radiological features, and tumor response by Response EvaluationCriteria for Solid Tumors V.1.1. Bronchoalveolar lavage fluid (BALF) samples were assessed by cell differential. Lung biopsy samples were evaluated by H&E staining and multiplex immunofluorescence (mIF), where available. **RESULTS:** Among 299 patients, 44 developed ICI pneumonitis (NSCLC: 5/205; melanoma: 1/94), and of these, 6 experienced chronic ICI pneumonitis. The overall incidence of chronic ICI pneumonitis was thus 2%. Of those who developed chronic ICI pneumonitis: the majority had NSCLC (5/6), all sustained disease control from ICIs, and none had other concurrent irAEs. Timing of chronic ICI pneumonitis development was variable (range: 0-50 months), and occurred at a median of 12 months post ICI start. Recrudescence of ICI pneumonitis occurred at a median of 6 weeks after initial steroid start (range: 3-12 weeks), with all patients requiring steroid reintroduction when tapered to ≤10 mg prednisone/equivalent. The median total duration of steroids was 37 weeks (range: 16-43+weeks). Re-emergence of radiographic ICI pneumonitis occurred in the same locations on chest CT, in most cases (5/6). All patients who developed chronic ICI pneumonitis had BALF lymphocytosis on cell differential and organising pneumonia on lung biopsy at initial ICI pneumonitis presentation, with persistent BALF lymphocytosis and brisk CD8+ infiltration on mIF at

pneumonitis re-emergence during steroid taper. **CONCLUSIONS:** A subset of patients who develop pneumonitis from ICIs will develop chronic ICI pneumonitis, that warrants long-term immunosuppression of ≥12 weeks, and has distinct clinicopathological features.

[Association of CD8 T Cell Apoptosis and EGFR Mutation in Non-Small Lung Cancer Patients](#)

 Chao Zhao 1 , Chunxia Su 2 , Xuefei Li 1 , Caicun Zhou 2

BACKGROUND: The abundance of tumor infiltrating CD8 T cells is an important parameter for antitumor effect of PD-1/PD-L1 immune checkpoint inhibitors, which is less in epidermal growth factor receptor (EGFR) mutation than wild-type non-small cell lung cancer (NSCLC). The mechanism still requires further study. **METHODS:** In total 190 surgical lung adenocarcinoma samples were included. EGFR mutation was detected using amplification-refractory mutation system. CD8 T cells and apoptosis were assessed by immunohistochemistry and immunofluorescence staining in tumor samples. Exosomes extracted from lung cancer cell lines with and without EGFR mutation were used to test the function of promoting apoptosis in vitro. **RESULTS:** The ratio of CD8 tumor infiltration lymphocytes was significantly lower in EGFR-mutant than in wild-type patients (P = 0.026). A higher ratio of apoptosis was also prone to occur in EGFR-mutant patients (P = 0.035). The distribution of apoptosis was not statistically associated with the ratio of CD8 TILs. An in vitro experiment indicated that exosomes secreted by EGFR-mutant non-small cell lung cancer cell lines PC9 and HCC827 were more capable of promoting CD8 T cell apoptosis than EGFR wild-type cell lines H1299 and SK-MES-1 (P = 0.007 and P = 0.010, respectively). **CONCLUSIONS:** Non-small cell lung cancer EGFR mutation could promote CD8 T cell apoptosis more than wild-type. Inhibiting CD8 + TILs apoptosis may strengthen immunotherapy effects in EGFR-mutant NSCLC patients.

[Neoadjuvant Immunotherapy for Non-Small Cell Lung Cancer - Current Concepts and Future Approaches](#)

 Dipesh Uprety 1 , Sumithra J Mandrekar 2 , Dennis Wigle 3 , Anja C Roden 4 , Alex A Adjei 5

Lung cancer is the leading cause of cancer-related deaths worldwide. Patients with resectable non-small cell lung cancer (NSCLC) are often treated with surgery and adjuvant chemotherapy. However, these patients continue to have a high risk of recurrence and death. Unfortunately, there has been little progress in the treatment of resectable NSCLC over the last several decades. Neoadjuvant therapy, which has been considered an approach to improve survival for resectable NSCLC patients, is a hotly debated topic. A systematic review of 32 randomized trials involving 10,000 patients demonstrated that there was no difference in survival between pre and post-operative chemotherapy. Because of such results, and the theoretical concern about resectable tumors progressing on relatively ineffective neoadjuvant chemotherapy and thus becoming unresectable, neoadjuvant chemotherapy fell out of favor and many clinicians preferred adjuvant chemotherapy post-surgery. Neoadjuvant therapy has however been revived in the last couple of years following emerging data from various ongoing trials suggesting that neoadjuvant immunotherapy may have significant efficacy and could potentially improve survival of patients with resectable NSCLC. In this review article, we discuss the evidence supporting the role of neoadjuvant immunotherapy in the multimodality management of resectable NSCLC. We summarize early results of ongoing clinical trials, and highlight the challenges in adopting a uniform definition of treatment "success." We address hurdles to be overcome in order to seek regulatory approval for neoadjuvant immunotherapy and establish it as a standard of care. Finally we provide some perspectives for the future.

[ALK-Rearranged Non-Small Cell Lung Cancer in 2020: Real-World Triumphs in an Era of Multigeneration ALK-Inhibitor Sequencing Informed by Drug Resistance Profiling](#)
Oncologist. 2020 Jun 18. doi: 10.1634/theoncologist.2020-0075. Online ahead of print.
Malinda Itchins 1   2   3 , Brandon Lau 4 , Amanda L Hudson 2   3 , et al.
https://pubmed.ncbi.nlm.nih.gov/32558067/

Since its discovery in 2007, we have seen the lives of patients diagnosed with advanced anaplastic lymphoma kinase (ALK)-rearranged non-small cell lung cancers (NSCLC) transform with the advent of molecular therapies with first-, second-, and third-generation ALK inhibitors now available in the clinic. Despite great gains in patient survival now measured in years and preserved quality of life with targeted therapies, drug resistance is unfortunately inevitably encountered in this rare and unique molecular subset of lung cancer, and patients will eventually succumb to the disease. As these patients are often young, fit, and never smokers, the clinical and scientific communities have aligned to expedite drug development and access. Drug resistance profiling and further strategies are being explored through clinical trials, including the evaluation of specific drug sequencing and combinations to overcome such resistance and promote patient longevity. The cases of this report focus on precision medicine and aim to portray the pertinent aspects to consider when treating ALK-rearranged NSCLC in 2020, an ever-shifting space. By way of case examples, this report offers valuable information to the treating clinician, including the evolution of systemic treatments and the management of oligo-progression and multisite drug resistance. With the maturation of real-world data, we are fortunate to be experiencing quality and length of life for patients with this disease surpassing prior expectations in advanced lung cancer. KEY POINTS: This report focuses on the importance of genetic analysis of serial biopsies to capture the dynamic therapeutic vulnerabilities of a patient's tumor, providing a perspective on the complexity of ALK tyrosine kinase inhibitor (ALKi) treatment sequencing. These case examples contribute to the literature on ALK-rearranged and oncogene addicted non-small cell lung cancer (NSCLC), providing a framework for care in the clinic. In oligo-progressive disease, local ablative therapy and continuation of ALKi postprogression should be considered with potential for sustained disease control. ALK G1202R kinase domain mutations (KDM), highly prevalent at resistance to second-generation ALKi resistances, may emerge in non-EML4-ALK variant 3 cases and is sensitive to third-generation lorlatinib. When in compound with one or more ALK KDMs, resistance to lorlatinib is expected. In the case of rampantly progressive disease, rebiopsy and redefining biology in a timely manner may be informative.

NSCLC - RADIOTHERAPY

[Quantifying the Interfractionalmotion of Esophagus Using Daily Cone Beam Computed Tomography With Oral Contrast During Radiotherapy for Locally Advanced Non-Small Cell Lung Cancer](#) Pract Radiat Oncol. 2020 Jun 28;S1879-8500(20)30163-6. doi: 10.1016/j.prro.2020.06.006. Online ahead of print. Bo Qiu 1 , Shi Pei Lu 2 , Bin Wang 2 , et al.
BACKGROUND AND PURPOSE: To quantify the interfractional motion of the esophagus during fractionated radiotherapy for locally advanced non-small cell lung cancer (NSCLC). **MATERIALS AND METHODS:** We registered simulation four-dimensional computed tomography (4DCT) and daily cone beam CT (CBCT), and documented the motion of the esophagus centroid at 5mm-interval slices in right-left (RL) and anterior-posterior (AP) directions. Oral barium sulfate was administrated during CBCT to help localize the esophagus. Thirty-five patients were enrolled. Thirty-five 4DCT scans, 595 CBCT scans and 25,970 slices were analyzed. The slice-derived motion values for all patients were presented as 2.5~97.5 percentiles and ranges stratified by segments. The magnitude of motion for each individual patient was defined as the standard deviation (SD) of daily motion values stratified by segments. Correlations between the magnitude of motion and clinical variables were explored. **RESULTS:** The 2.5~97.5 percentiles of RL/AP motion were -4.2~7.1/-4.4~5.1, -10.3~6.0/-4.3~3.8, -8.7~5.5/ -6.4~2.8

and -9.1~4.7/-5.8~3.3mm for cervical, proximal, middle and distal thoracic esophagus respectively. The interfractional motion was direction- and location-dependent. The magnitude of RL motion was greater than that of AP motion for the four segments (p<0.05). In RL direction, the magnitude of motion was greater for middle thoracic esophagus than for cervical (median SD, 2.7 vs. 2.0 mm, p=0.001) and proximal thoracic esophagus (median SD, 2.7 vs. 2.1 mm, p=0.002). Patients with right lung tumor and bulky lymph nodes tended to display greater RL esophageal motion. **CONCLUSIONS:** The interfractional motion of the esophagus can be considerable during radiotherapy in locally advanced NSCLC, especially for middle thoracic esophagus in RL direction. Strategies to minimize the effect of interfractional esophageal motion on dosimetry should be considered.

[**The Impact of 4DCT-ventilation Imaging-Guided Proton Therapy on Stereotactic Body Radiotherapy for Lung Cancer**](#) Radiol Phys Technol. 2020 Jun 14. doi: 10.1007/s12194-020-00572-5. Online ahead of print.Yoshiro Ieko 1   2 , Noriyuki Kadoya 3 , Takayuki Kanai 1   4 , et al. Functional lung avoidance during radiotherapy can help reduce pulmonary toxicity. This study assessed the potential impact of four-dimensional computed tomography (4DCT)-ventilation imaging-guided proton radiotherapy (PT) on stereotactic body radiotherapy (SBRT) by comparing it with three-dimensional conformal radiotherapy (3D-CRT) and volumetric modulated arc therapy (VMAT), which employ photon beams. Thirteen lung cancer patients who received SBRT with 3D-CRT were included in the study. 4DCT ventilation was calculated using the patients' 4DCT data, deformable image registration, and a density-change-based algorithm. Three functional treatment plans sparing the functional lung regions were developed for each patient using 3D-CRT, VMAT, and PT. The prescribed doses and dose constraints were based on the Radiation Therapy Oncology Group 0618 protocol. We evaluated the region of interest (ROI) and functional map-based dose-function metrics for 4DCT ventilation and the irradiated dose. Using 3D-CRT, VMAT, and PT, the percentages of the functional lung regions that received ≥ 5 Gy (fV5) were 26.0%, 21.9%, and 10.7%, respectively; the fV10 were 14.4%, 11.4%, and 9.0%, respectively; and fV20 were 6.5%, 6.4%, and 6.6%, respectively, and the functional mean lung doses (fMLD) were 5.6 Gy, 5.2 Gy, and 3.8 Gy, respectively. These results indicated that PT resulted in a significant reduction in fMLD, fV5, and fV10, but not fV20. The use of PT reduced the radiation to highly functional lung regions compared with those for 3D-CRT and VMAT while meeting all dose constraints.

SMALL CELL LUNG CANCER - SCLC

[**The Role of Immune Checkpoint Inhibitors in the Treatment of Extensive-Stage Extrapulmonary Small Cell Carcinoma**](#) Cureus. 2020 Jun 27;12(6):e8862. doi: 10.7759/cureus.8862. Ragia Aly 1 , Sachin Gupta 2 , Rashmika Potdar 3
Small cell carcinoma is a type of highly aggressive poorly differentiated neuroendocrine tumor that can arise from multiple organs, including but not limited to bronchial tissue, pancreas, gastrointestinal tract, and genitourinary system. The most commonly studied type is small cell lung cancer (SCLC) which carries the worst prognosis among lung cancers. After multiple promising clinical trials, the National Comprehensive Cancer Network has recently added atezolizumab and durvalumab in combination with platinum-based chemotherapy/etoposide to the first-line treatment regimen for extensive-stage SCLC (ES-SCLC). Meanwhile, the recommended treatment for extrapulmonary small cell carcinoma (EPSCC) remains unchanged. In this review, we try to explore the role of immunotherapy in the treatment of EPSCC.

[**IMpower, CASPIAN, and More: Exploring the Optimal First-Line Immunotherapy for Extensive-Stage Small Cell Lung Cancer**](#) J Hematol Oncol. 2020 Jun 5;13(1):69. doi: 10.1186/s13045-020-00898-y. Chengliang Huang 1   2 , Gregory N Gan 3   4 , Jun Zhang 5   6

The life expectancy of extensive-stage small cell lung (ES-SCLC) cancer patients has not improved in the last 2-3 decades until two recent trials (CASPIAN and IMpower133) showing the addition of anti-programmed death ligand (PD-L1) therapy to chemotherapy has survival benefit over chemotherapy alone. However, such benefit is relatively small and was not even observed in some other trials using immunotherapy, raising the question of optimal chemoimmunotherapy combination in the 1st-line setting for ES-SCLC. Here, we discussed several thought-provoking questions with the focus on IMpower133 and CASPIAN trials.

Effect of Lymph Node Assessment on Outcomes in Surgery for Limited Stage Small Cell Lung Cancer Ann Thorac Surg. 2020 Jun 13;S0003-4975(20)30930-9. doi: 10.1016/j.athoracsur.2020.04.117. Online ahead of print. A Justin Rucker 1 , Vignesh Raman 2 , Oliver K Jawitz 2 , Soraya L Voigt 2 , Betty C Tong 2 , Thomas A D'Amico 2 , David H Harpole 2
BACKGROUND: The National Comprehensive Cancer Network guidelines recommend surgery for limited stage small cell lung cancer (SCLC). However, there is no literature on minimum acceptable lymph node retrieval in surgery for SCLC. **METHODS:** The National Cancer Database was queried for adult patients undergoing lobectomy for limited stage (cT1-2N0M0) SCLC from 2004-2015. Patients with unknown survival, staging, or nodal assessment and those who received neoadjuvant therapy were excluded. The number of lymph nodes assessed was studied both as a continuous variable and as a categorical variable stratified into distribution quartiles. The primary outcome was overall survival and the secondary outcome was pathologic nodal upstaging. **RESULTS:** A total of 1051 patients met study criteria. In multivariable analysis, only a retrieval of 8-12 nodes was associated with a significant survival benefit (hazard ratio [HR] 0.73; 95%CI 0.56-0.98). However, when modeled as a continuous variable, there was no association between number of nodes assessed and survival (HR 1.00; 95%CI 0.98-1.02). The overall rate of pathologic nodal upstaging was 19%. Modeled as a continuous variable, greater than 7 lymph nodes assessed at time of resection was significantly associated with nodal upstaging in multivariable regression (odds ratio [OR] 1.03; 95%CI 1.01-1.06). **CONCLUSION:** In this study, there was no clear difference in survival based on increasing the number of lymph nodes assessed during lobectomy for limited stage SCLC. However, the number of retrieved lymph nodes was associated with pathologic nodal upstaging. Therefore, patients may benefit from retrieval of greater than 7 lymph nodes during lobectomy for SCLC.

Is There a Role for Hypofractionated Thoracic Radiotherapy in Limited-Stage Small Cell Lung Cancer? A Propensity Score Matched Analysis Int J Radiat Oncol Biol Phys. 2020 Jun 13;S0360-3016(20)31249-9. doi: 10.1016/j.ijrobp.2020.06.008. Online ahead of print. Sondos Zayed 1 , Hanbo Chen 1 , Emma Ali 2 , George B Rodrigues 1 , Andrew Warner 1 , David A Palma 1 , Alexander V Louie 3
INTRODUCTION: Various radiation schedules are used in concurrent chemoradiotherapy for limited-stage small cell lung cancer (LS-SCLC). As there is currently no randomized evidence comparing hypofractionated (HFRT) and conventionally-fractionated radiotherapy (CFRT), the aim of this study was to compare overall survival (OS), progression-free survival (PFS), and toxicity of HFRT and CFRT in LS-SCLC. **METHODS**: LS-SCLC patients treated between 2000-2013 with HFRT (40Gy/15, 45Gy/15, 45Gy/20 fractions) or CFRT (60Gy/30 or 66Gy/33 fractions) were included. Propensity scores were generated using a multivariable logistic regression model. Patients were matched on a 1:1 ratio with a caliper distance of 0.20. OS and PFS were estimated by the Kaplan-Meier method and compared using log-rank tests. As a sensitivity analysis, univariable and multivariable Cox regression was performed including all patients without matching. Logistic regression was performed to identify predictors of pulmonary and esophageal adverse events. **RESULTS:** In the overall group of 117 patients, there were significant baseline differences between the HFRT and CFRT cohorts. Patients who received CFRT were

older, smoked more often concurrently with treatment, had higher ECOG performance status, different T and N stage patterns, and more commonly received concurrent chemoradiotherapy and prophylactic cranial irradiation. After propensity score matching for these differences, 72 patients were included, 36 in the HFRT and CFRT cohorts respectively. There was no difference in OS (P=0.724), PFS (P=0.862), any pulmonary (P=0.350), or esophageal (P=0.097) adverse events between cohorts. Skin adverse events were significantly higher for CFRT (41.7%) compared with HFRT (16.7%, P=0.020). Multivariable Cox regression also revealed no differences in OS (P=0.886) or PFS (P=0.717) between all HFRT and CFRT patients, without matching. No grade 5 adverse events were observed. **CONCLUSION:** In LS-SCLC patients, HFRT was associated with comparable survival and toxicity outcomes and may be considered as an alternative to CFRT, should its efficacy be confirmed in prospective studies.

[**Determination of Endothelial Nitric Oxide Synthase Gene Polymorphism and Plasma Asymmetric Dimethyl Arginine Concentrations in Patients With Lung Cancer**](#) Eurasian J Med. 2020 Jun;52(2):185-190. doi: 10.5152/eurasianjmed.2020.19220. Epub 2020 Jun 5. Zafer Bayraktutan 1 , Ahmet Kiziltunc 1 , Ebubekir Bakan 1 , Hamit Hakan Alp 2

OBJECTIVE: Genetic factors can contribute to both the occurrence and development of lung cancer. This study aimed to investigate endothelial nitric oxide synthase (eNOS) G894T and T-786C polymorphisms and plasma asymmetric dimethylarginine (ADMA) levels of lung cancer patients in comparison with healthy subjects. **MATERIALS AND METHODS:** A total of 200 subjects, 100 patients with lung cancer and 100 healthy volunteers were included in this study. To determine eNOS gene polymorphisms, we collected and analyzed blood samples with polymerase chain reaction (PCR). Plasma ADMA levels were evaluated by high-performance liquid chromatography (HPLC). **RESULTS:** The difference in gene polymorphisms between lung cancer patients and healthy controls were insignificant. However, lung cancer patients had statistically significantly higher plasma ADMA levels than healthy controls. The patients and control groups with CC polymorphisms and TT polymorphisms on eNOS T-786C and G894T gene regions had higher plasma ADMA levels. The CC polymorphisms and plasma ADMA levels were higher in patients with small-cell lung cancer compared to those in patients with non-small-cell lung cancer. **CONCLUSION:** Although eNOS gene polymorphisms had no significant difference between lung cancer patients and healthy controls, plasma ADMA levels were higher in lung cancer patients compared to healthy controls. Our study suggests that CC genotypes and elevated plasma ADMA levels might be associated with small-cell lung cancer.

[**Systemic Therapy of Extensive Stage Small Cell Lung Cancer in the Era of Immunotherapy**](#)
Curr Treat Options Oncol. 2020 Jun 29;21(8):64. doi: 10.1007/s11864-020-00762-8. Meera Ragavan 1 , Millie Das 2   3

In March 2019, the FDA approved the use of the anti-programmed death ligand 1 (PD-L1) antibody atezolizumab, as a first-line treatment option in combination with platinum-etoposide (PE) for patients with extensive stage small cell lung cancer (ED SCLC) based upon the results of the IMpower133 trial. More recently, the FDA approved the anti-PD-L1 antibody durvalumab in March 2020 , also in the frontline setting for SCLC based upon the results of the CASPIAN trial. Both these trials demonstrated a small, but significant overall survival (OS) benefit with the addition of a PD-L1 antibody to standard chemotherapy in the treatment of ED SCLC, thereby altering the treatment paradigm for this aggressive disease. Previously, the FDA had approved the anti-PD1 antibodies nivolumab and pembrolizumab as single-agent third-line treatment options based upon encouraging phase 1/2 data in patients with relapsed SCLC who had not received prior immunotherapy (IO). Despite these recent advances, the overall benefit of IO in SCLC remains somewhat disappointing in comparison with the results seen in non-small cell lung cancer (NSCLC). To date, no reliable biomarkers exist to predict responsiveness to IO in SCLC, and the utility of second- or third-line immunotherapy is questionable in patients who have received IO as part

of first-line treatment. There has also been minimal success in identifying targetable mutations in SCLC. Novel approaches include combination approaches with IO, including PARP inhibitors and CDK inhibitors. Few ongoing trials, however, have enrolled patients who have received frontline immunotherapy given the only recent change in standard of care. Consequently, the results of current trials evaluating second- and third-line therapies need to be interpreted and translated into clinical practice with caution. The most significant challenge in SCLC remains the identification of molecular targets for which drugs can be developed that can improve survival over the current standard of care.

[Clinical Characteristics and Prognostic Factors of Surgically Resected Combined Small Cell Lung Cancer: A Retrospective Study](#) Lung Cancer. 2020 Jun 17;146:244-251. doi: 10.1016/j.lungcan.2020.06.021. Online ahead of print.Yuqiong Lei 1 , Hui Feng 2 , Huiping Qiang 1 , Zhanxian Shang 3 , Qing Chang 1 , Jialin Qian 1 , Yanwei Zhang 1 , Runbo Zhong 1 , Xiaohong Fan 4 , Tianqing Chu 5

OBJECTIVES: Small cell lung cancer (SCLC) is the most malignant lung cancer. Some of them are mixed with non-small cell lung cancer(NSCLC, Non SCLC),which are called combined small cell lung cancer (C-SCLC).Due to the difficulty of pathological diagnosis and the complexity of treatment, studies of C-SCLC have just been rising in recent years. This study is to evaluate the clinical and pathologic characteristics of C-SCLC. **METHODS:** Stage I-IIIa C-SCLC patients who received radical R0 surgery between 2009-2018 in Shanghai Chest Hospital were enrolled. Clinical characteristics and prognosis were analyzed. **RESULTS:** Totally 181 patients were included, most of them were small cell combined with large cell neuroendocrine components(SCLC/LCNEC,58.0 %,N = 105),then with adenocarcinoma (SCLC/ADC:13.8 %,N = 25),and finally with squamous cell carcinoma(SCLC/SCC:13.3 %,N = 24).Median DFS and OS of C-SCLC patients underwent radical surgery were 32.5 and 49.7 months.1,3 and 5 years DFS rates of the entire cohort were 68.5 %,32.6 % and 16.0 %,respectively. Patients with SCLC/LCNEC had longer DFS (44.1 m vs. 20.4 m, p = 0.040) and longer OS trend (62.1 m vs. 33.2 m, p = 0.122).Groups of whether tumor invaded the pleura(p = 0.028 and p = 0.050),lymph node stage(p = 0.029 and p = 0.010) and the courses of adjuvant chemotherapy(p = 0.011 and p = 0.001) had statistical differences on DFS and OS. **CONCLUSIONS:** SCLC/LCNEC was the most common type of C-SCLC. Patients' DFS and OS were also longer than other combined types. Adjuvant chemotherapy for SCLC is still the main treatment for surgical C-SCLC. Further studies are needed to clarify the clinical characteristics and prognosis of C-SCLC.

[Impact of Amrubicin Monotherapy as Second-Line Chemotherapy on Outcomes in Elderly Patients With Relapsed Extensive-Disease Small-Cell Lung Cancer](#) Cancer Manag Res. 2020 Jun 23;12:4911-4921. doi: 10.2147/CMAR.S255552. eCollection 2020. Satoshi Igawa 1 , Taihei Ono 1 , Masashi Kasajima 1 , Hideaki Manabe 1 , et al.

PURPOSE: Amrubicin (AMR) is an anticancer drug for patients with relapsed small-cell lung cancer (SCLC). However, the efficacy of AMR in elderly patients with relapsed SCLC after chemotherapy by carboplatin plus etoposide (CE) has not been sufficiently evaluated. **PATIENTS AND METHODS:** The medical records of patients with relapsed SCLC who received AMR as second-line chemotherapy were retrospectively reviewed, and their treatment outcomes were evaluated. **RESULTS:** Forty-one patients with a median age of 76 years were analyzed. The overall response rate was 26.8%. Median progression-free survival (PFS) and overall survival (OS) were 3.5 and 8.1 months, respectively. While the median PFS of 4.7 and 2.8 months in the sensitive relapse and the refractory relapse group differed significantly (P=0.043), respectively, the median OS of 10.7 and 6.8 months in the respective relapse groups did not indicate a statistically significant difference (P=0.24). The median PFS in a group with a modified Glasgow prognostic score (mGPS) of 0 and a group with a mGPS 1 or 2 were 4.5 and 1.6 months (P=0.052), respectively, and the median OS in the respective mGPS groups were 10.7 and 4.4 months

(P=0.034). Multivariate analysis identified good performance status, limited disease, and mGPS 0 as favorable independent predictors of PFS and OS of AMR monotherapy. Grade 3 or higher neutropenia was observed in 23 patients (56%), and febrile neutropenia was observed in nine patients (22%). Non-hematological toxic effects were relatively mild, and pneumonitis and treatment-related deaths were not observed. **CONCLUSION:** AMR is an effective and feasible regimen for elderly patients with relapsed SCLC after CE therapy.

[Advances in Small-Cell Lung Cancer (SCLC) Translational Research](#) Cold Spring Harb Perspect Med. 2020 Jun 8;a038240. doi: 10.1101/cshperspect.a038240. Online ahead of print. Benjamin J Drapkin 1 , Charles M Rudin 2

Over the past several years, we have witnessed a resurgence of interest in the biology and therapeutic vulnerabilities of small-cell lung cancer (SCLC). This has been driven in part through the development of a more extensive array of representative models of disease, including a diverse variety of genetically engineered mouse models and human tumor xenografts. Herein, we review recent progress in SCLC model development, and consider some of the particularly active avenues of translational research in SCLC, including interrogation of intratumoral heterogeneity, insights into the cell of origin and oncogenic drivers, mechanisms of chemoresistance, and new therapeutic opportunities including biomarker-directed targeted therapies and immunotherapies. Whereas SCLC remains a highly lethal disease, these new avenues of translational research, bringing together mechanism-based preclinical and clinical research, offer new hope for patients with SCLC.

PALLIATIVE AND SUPPORTIVE CARE

[The Association Between History of Traumatic Events and Health-Related Quality of Life Among Lung Cancer Patients](#) J Psychosoc Oncol. 2020 Jun 29;1-8. doi: 10.1080/07347332.2020.1780364. Online ahead of print. René Bayley-Veloso 1   2 , Yvette Z Szabo 3 , Elizabeth Cash 1   4   5 , et al.

PURPOSE: Promoting health-related quality of life (HRQOL) is a primary goal of lung cancer treatment. Trauma history and distress can negatively impact HRQOL. **DESIGN:** A cross-sectional design examined the associations of trauma history, cancer-specific distress, and HRQOL.Sample/Method: Sixty lung cancer patients completed questionnaires on trauma history including the number and severity of traumatic events experienced. Cancer-specific distress, HRQOL, and depression were also reported. **FINDINGS**: As hypothesized, trauma history and cancer-specific distress were negatively associated with HRQOL (all r's > -.27). Depression emerged as a confound in the association between cancer-specific distress and HRQOL. **CONCLUSIONS:** Retrospectively-reported trauma was linked with poorer HRQOL in lung cancer patients. **IMPLICATIONS:** Interventions aimed at improving lung cancer patients' HRQOL should consider the possible role of trauma history (both frequency and distress).

[Claims Identification of Patients With Severe Cancer-Related Symptoms](#) Am J Manag Care. 2020 Jun 1;26(6):e191-e197. doi: 10.37765/ajmc.2020.43495. Richard W DeClue, Dana Drzayich Antol, Adrianne W Casebeer 1 , Todd Michael, Marina Sehman, Andrew Renda, Sarika Ogale, Stephen Stemkowski, Bryan Loy

OBJECTIVES: The goal of this study was to establish a claims-based mechanism for identifying patients with metastatic non-small cell lung cancer (mNSCLC) and high levels of patient-reported cancer-related symptoms who could benefit from engagement with health care programs. **STUDY DESIGN:** A cross-sectional survey of patients with mNSCLC was conducted from July 2017 to May 2018. Surveys were mailed to patients who were within 3 months of cancer treatment and enrolled in a Medicare Advantage health plan. **METHODS:** Pain, fatigue, and sleep disturbance were measured using the Patient-Reported Outcomes Measurement Information System. Depression was assessed using the Patient

Health Questionnaire-2. Medical claims were linked to survey results to identify comorbidities and assess preindex health care resource utilization. Cluster analysis was used to differentiate patients based on patient-reported pain interference, pain intensity, depression, and sleep disturbance. Logistic regression was used to identify claims-based measures associated with more severe symptoms. **RESULTS:** For 698 respondents, 2 distinct symptom clusters were identified: a less severe (38.4%) cluster and a more severe (61.6%) cluster. Patients in the more severe cluster were younger, were more frequently dually eligible for Medicare and Medicaid, and more frequently had prescription fills for opioids. Claims-based factors associated with the more severe cluster included 2 or more 30-day fills for opioids in the prior 6 months, age younger than 75 years, depression diagnosis or antidepressants, bone metastases, and pain-related outpatient visits. **CONCLUSIONS:** The claims-based factors associated with the severe symptom cluster can enable identification of patients with mNSCLC who could benefit from clinical outreach programs to enhance the care and support provided to these patients.

[Predictive Model of Psychological Distress in Patients With Lung Cancer: A Cross-sectional Study](#)
Cancer Nurs. 2020 Jun 11. doi: 10.1097/NCC.0000000000000837. Online ahead of print. Xiao-Qing L 1 , Bing-Qing Wang, Huan-Huan Tong, Shan-Shan Liu, Hsin-Yi Jean Tang, Jing-Fang Hong
BACKGROUND: Patients with lung cancer suffer from significant psychological distress. The underlying theoretical model that may explain what predicts or mediates the degree of psychological distress has not been elucidated. **OBJECTIVES**: To describe the incidence of psychological distress in patients with lung cancer and to test a predictive theoretical model of psychological distress based on symptom burden, type D personality, social support, and intrusive thoughts. **METHODS:** Three hundred eighty-nine patients with stages I to IV lung cancer were recruited. Participants completed a battery of scales, including measures of psychological distress, symptom burden, type D personality, perceived social support, intrusive thoughts, and demographic and clinical characteristics. The predictive theoretical model was tested using structural equation modeling. **RESULTS:** Experiencing clinically significant psychological distress was reported by 63.75% of participants. Consistent with the social cognitive processing model, symptom burden, type D personality, social support, and intrusive thoughts all significantly and directly predicted the level of psychological distress in patients with lung cancer. Moreover, intrusive thoughts mediated the effects of type D personality and symptom burden on psychological distress; social support and symptom burden mediated the effects of type D personality on psychological distress. **CONCLUSIONS:** The majority of the participants experienced psychological distress at a clinically significant level. Intrusive thoughts and social support mediated the effects of type D personality and symptom burden on psychological distress. **IMPLICATIONS FOR PRACTICE:** Patients with type D personality and symptom burden should be identified. Interventions for targeting social support and intrusive thoughts might ultimately reduce their psychological distress.

COMPLEMENTARY & ALTERNATIVE THERAPY

[Berberine Chloride Suppresses Non-Small Cell Lung Cancer by Deregulating Sin3A/TOP2B Pathway in Vitro and in Vivo](#)
Cancer Chemother Pharmacol. 2020 Jun 30. doi: 10.1007/s00280-020-04050-y. Online ahead of print. Jian Chen 1 2 3 4 , Xiaofei Huang 4 , Cheng Tao 1 2 3 , Li Wang 5 , Zide Chen 1 , Xinping Li 2 3 , Qiang Zeng 1 2 3 , Min Ma 6 7 8 , Ren Zhang 9 10 , Zhengzhi Wu 11 12
PURPOSE: Berberine chloride (BBC) is a well-known plant isoquinoline alkaloid derived from Berberis aristata. In this study, we aim to explore the effect of BBC on non-small cell lung cancer (NSCLC), and further expound the underlying mechanism of BBC induces NSCLC cell death in vitro and in vivo. **METHODS:** CCK-8 assay and colony formation assay were used to test the viability and colony formation ability of NSCLC cells. Apoptosis analysis was used to analyze the apoptotic cells. siRNAs

were utilized to disturb the expression of Sin3A. qPCR and Western blot analysis were employed to determine mRNA and protein levels of related genes and proteins. Tumor xenografts model was used for in vivo detection. **RESULTS:** BBC inhibited the proliferation and colony formation of human NSCLC cells in a dose- and time-dependent manner. In addition, BBC induced DNA double-stranded breaks (DSBs) through downregulating TOP2B level, leading to apoptosis in human NSCLC cells. The Chip-seq data of A549 cells obtained from the ENCODE consortium indicate that Sin3A binds on the promoters of TOP2B. Knockdown of Sin3A led to downregulation of TOP2B in human NSCLC cells. Furthermore, BBC decreased Sin3A expression and shortened the half-life of Sin3A, results in downregulation of TOP2B in human NSCLC cells. **CONCLUSION:** In this study, we demonstrated a new mechanism that BBC suppresses human NSCLC by deregulating Sin3A/TOP2B pathway, leading to DNA damage and apoptosis in human NSCLC in vitro and in vivo.

[End-to-End Models to Imitate Traditional Chinese Medicine Syndrome Differentiation in Lung Cancer Diagnosis: Model Development and Validation](#) JMIR Med Inform. 2020 Jun 16;8(6):e17821. doi: 10.2196/17821. Ziqing Liu # 1 2 , Haiyang He # 3 , Shixing Yan 3 , Yong Wang 4 , Tao Yang 2 , Guo-Zheng Li 1

BACKGROUND: Traditional Chinese medicine (TCM) has been shown to be an efficient mode to manage advanced lung cancer, and accurate syndrome differentiation is crucial to treatment. Documented evidence of TCM treatment cases and the progress of artificial intelligence technology are enabling the development of intelligent TCM syndrome differentiation models. This is expected to expand the benefits of TCM to lung cancer patients. **OBJECTIVE:** The objective of this work was to establish end-to-end TCM diagnostic models to imitate lung cancer syndrome differentiation. The proposed models used unstructured medical records as inputs to capitalize on data collected for practical TCM treatment cases by lung cancer experts. The resulting models were expected to be more efficient than approaches that leverage structured TCM datasets. **METHODS:** We approached lung cancer TCM syndrome differentiation as a multilabel text classification problem. First, entity representation was conducted with Bidirectional Encoder Representations from Transformers and conditional random fields models. Then, five deep learning-based text classification models were applied to the construction of a medical record multilabel classifier, during which two data augmentation strategies were adopted to address overfitting issues. Finally, a fusion model approach was used to elevate the performance of the models. **RESULTS:** The F1 score of the recurrent convolutional neural network (RCNN) model with augmentation was 0.8650, a 2.41% improvement over the unaugmented model. The Hamming loss for RCNN with augmentation was 0.0987, which is 1.8% lower than that of the same model without augmentation. Among the models, the text-hierarchical attention network (Text-HAN) model achieved the highest F1 scores of 0.8676 and 0.8751. The mean average precision for the word encoding-based RCNN was 10% higher than that of the character encoding-based representation. A fusion model of the text-convolutional neural network, text-recurrent neural network, and Text-HAN models achieved an F1 score of 0.8884, which showed the best performance among the models. **CONCLUSIONS:** Medical records could be used more productively by constructing end-to-end models to facilitate TCM diagnosis. With the aid of entity-level representation, data augmentation, and model fusion, deep learning-based multilabel classification approaches can better imitate TCM syndrome differentiation in complex cases such as advanced lung cancer.

MISCELLANEOUS WORKS

[Core Microbiota in Central Lung Cancer With Streptococcal Enrichment as a Possible Diagnostic Marker](#) Arch Bronconeumol. 2020 Jun 30;S0300-2896(20)30192-7. doi: 10.1016/j.arbres.2020.05.034.

Online ahead of print. [Article in English, Spanish] Salvador Bello 1 , José J Vengoechea 2 , Manuel Ponce-Alonso 3 , et al.

BACKGROUND: Dysbiosis in lung cancer has been underexplored. The aim of this study was to define the bacterial and fungal microbiota of the bronchi in central lung cancer and to compare it with that of the oral and intestinal compartments. **METHODS:** Twenty-five patients with central lung cancer and sixteen controls without antimicrobial intake during the previous month were recruited. Bacterial and fungal distribution was determined by massive sequencing of bronchial biopsies and saliva and faecal samples. Complex computational analysis was performed to define the core lung microbiota. **RESULTS:** Affected and contralateral bronchi of patients have almost identical microbiota dominated by Streptococcus, whereas Pseudomonas was the dominant genera in controls. Oral and pulmonary ecosystems were significantly more similar in patients, probably due to microaspirations. Streptococcal abundance in the bronchi differentiated patients from controls according to a ROC curve analysis (90.9% sensitivity, 83.3% specificity, AUC=0.897). The saliva of patients characteristically showed a greater abundance of Streptococcus, Rothia, Gemella and Lactobacillus. The mycobiome of controls (Candida) was significantly different from that of patients (Malassezia). Cancer patients' bronchial mycobiome was similar to their saliva, but different from their contralateral bronchi. **CONCLUSIONS:** The central lung cancer microbiome shows high levels of Streptococcus, and differs significantly in its composition from that of control subjects. Changes are not restricted to tumour tissue, and seem to be the consequence of microaspirations from the oral cavity. These findings could be useful in the screening and even diagnosis of this disease.

[The Academic Facility Type Is Associated With Improved Overall Survival for Early Stage Lung Cancer](#)
Ann Thorac Surg. 2020 Jun 29;S0003-4975(20)31015-8. doi: 10.1016/j.athoracsur.2020.05.051. Online ahead of print. Robert E Merritt 1 , Mahmoud Abdel-Rasoul 2 , Morgan Fitzgerald 3 , Desmond M D'Souza 3 , Peter J Kneuertz 3

BACKGROUND: Early stage Non-small cell lung cancer (NSCLC) is potentially curable with surgical resection. The overall survival rate for early stage NSCLC may be determined by the healthcare facility type where patients receive their lung cancer treatment. **METHODS:** A total of 103,748 cases with the American Joint Committee on Cancer (AJCC) clinical stage I and II NSCLC that were reported to the National Cancer Database at over 1,150 facilities were analyzed in this study. Healthcare facilities were dichotomized into the community and academic facility types. Marginal multivariable Cox proportional hazard models were used to evaluate differences in overall survival. Propensity score methodology with inverse probability of treatment weighting was used to adjust for facility volume and patient related baseline differences between facility types. **RESULTS:** Patients with early stage NSCLC who were treated at academic facility types had a significantly better median overall survival (63.2 months) compared to patients who received care at community healthcare facilities (54.2 months) [HR= 0.86 (95% CI:0.82-0.91) (p<0.0001)]. The surgical quality outcomes for NSCLC surgery, including 30-day mortality, 90-day mortality, and the median number of lymph nodes removed were significantly better for patients treated at the academic facility types. **CONCLUSIONS:** Patients with early stage NSCLC who were treated at academic facility types had a significantly higher overall median survival compared to community facility types. The short-term surgical quality outcomes were significantly better for patients who underwent surgery for early stage NSCLC at academic facility types.

[COVID-19 in Patients With Lung Cancer](#)
Ann Oncol. 2020 Jun 16;S0923-7534(20)39894-X. doi: 10.1016/j.annonc.2020.06.007. Online ahead of print. Jia Luo 1 , Hira Rizvi 2 , Isabel R Preeshagul 1 , et al.

BACKGROUND: Patients with lung cancers may have disproportionately severe COVID-19 outcomes. Understanding the patient-specific and cancer-specific features that impact severity of COVID-19 may

inform optimal cancer care during this pandemic. **PATIENTS AND METHODS:** We examined consecutive patients with lung cancer and confirmed diagnosis of COVID-19 (n=102) at a single center from March 12-May 6, 2020. Thresholds of severity were defined a priori as hospitalization, ICU/intubation/DNI (a composite metric of severe disease including ICU stay, intubation and invasive mechanical ventilation, and/or transition to do not intubate [DNI]), or death. Recovery was defined as >14 days from COVID-19 test and >3 days since symptom resolution. HLA alleles were inferred from MSK-IMPACT (n=46) and compared to controls with lung cancer and no known non-COVID-19 (n=5166). **RESULTS:** COVID-19 was severe in patients with lung cancer (62% hospitalized, 25% died). Although severe, COVID-19 accounted for a minority of overall lung cancer-deaths during the pandemic (11% overall). Determinants of COVID-19 severity were largely patient-specific features, including smoking status and chronic obstructive pulmonary disease (Odds ratios for severe COVID-19 2.9, 95% CI 1.07-9.44 comparing the median [23.5 pack-years] to never and 3.87, 95% CI 1.35-9.68, respectively). Cancer-specific features, including prior thoracic surgery/radiation and recent systemic therapies did not impact severity. HLA supertypes were generally similar in mild or severe cases of COVID-19 compared to non-COVID-19 controls. Most patients recovered from COVID-19, including 25% patients initially requiring intubation. Among hospitalized patients, hydroxychloroquine did not improve COVID-19 outcomes. **CONCLUSION:** COVID-19 is associated with high burden of severity in patients with lung cancer. Patient-specific features, rather than cancer-specific features or treatments, are the greatest determinants of severity.

[Treatment Decision Drivers in Stage III Non-Small-Cell Lung Cancer: Outcomes of a Web-Based Survey of Oncologists in the United States](#) JCO Oncol Pract. 2020 Jun 18;JOP1900781. doi: 10.1200/JOP.19.00781. Online ahead of print. Ion Cotarla 1 , Marnie L Boron 1 , Shawna L Cullen 1 , Daryl S Spinner 2 , Eric C Faulkner 2 , Marissa C Carroll 2 , Surbhi Shah 2 , Adam Yagui-Beltran 1
PURPOSE: We conducted a cross-sectional survey of practicing medical oncologists in the United States to obtain insight into physician and patient treatment decision making in stage III non-small-cell lung cancer (NSCLC). **METHODS:** A convenience sample of 150 oncologists completed a 38-question Web-based survey in January 2019. **RESULTS:** Surveyed oncologists (82% community based) had an average of 15 years of clinical experience and had treated an average of 20 patients newly diagnosed with stage III NSCLC in the previous 6 months. Oncologists reported presenting 55% of their patients with stage III NSCLC to tumor boards. For patients with new unresectable stage III NSCLC seen in the previous 6 months, concurrent chemoradiation therapy (cCRT) was reported as the initial treatment in an average of 48% of patients. The most frequent reason for delays in starting the initial chosen treatment was insurance preauthorization processes (reported by 65% of oncologists). A total of 55% of all patients with unresectable stage III NSCLC who received cCRT went on to receive consolidation immunotherapy; for patients who received consolidation chemotherapy after cCRT, the rate of immunotherapy was lower (42%). Biomarker test results were given as the reason for oncologists not recommending immunotherapy after cCRT in approximately a quarter of cases. The 112 oncologists with eligible patients who declined immunotherapy reported previous treatment fatigue as the reason in 34% of patients and insurance challenges in 19% of patients. **CONCLUSION:** Oncologists reported notable deviations from treatment guidelines for stage III NSCLC. Our findings highlight important opportunities to improve decision making and the coordination of care in stage III NSCLC.

[Outcomes Among Homeless Patients With Non-Small-Cell Lung Cancer: A County Hospital Experience](#) JCO Oncol Pract. 2020 Jun 11;JOP1900694. doi: 10.1200/JOP.19.00694. Online ahead of print.
Kyle F Concannon 1 , James H Thayer 1 , Qian V Wu 2 , Isaac C Jenkins 2 , Christina S Baik 1   3 , Hannah M Linden 1   3

PURPOSE: Lung cancer remains the leading cause of cancer death in the United States, with outcomes likely worsened by the presence of poorer outcomes among vulnerable populations such as the homeless. We hypothesized that homeless patients experience delays in biopsy, decreased appointment adherence, and increased overall mortality rates. **METHODS:** We conducted a retrospective electronic medical record-based review of all patients with non-small-cell lung cancer (NSCLC; N = 133) between September 2012 and September 2018 at an academic county hospital in Seattle, Washington. **RESULTS:** Of the 133 patients treated for NSCLC, 22 (17%) were homeless at the time of their treatment. Among homeless patients with localized lung cancer, the mean time from radiographic finding to biopsy was 248 days, compared with 116 days among housed patients (P = .37). Homeless patients with advanced disease missed a mean of 26% of appointments in the year after diagnosis, compared with 16% among housed patients (P = .03). Homeless patients with advanced NSCLC had a median survival of 0.58 years, versus 1.30 years in housed patients (P = .48). **CONCLUSION:** To our knowledge, this is the first US study comparing outcomes among homeless and housed patients with NSCLC within the same institution; we found homeless patients had longer delays to biopsy, increased rates of missed appointments, and a trend toward decreased survival. This study shows potential areas where interventions could be implemented to improve lung cancer outcomes in this patient population.