



# Caring Ambassadors Lung Cancer Program

## Literature Review, May 2021

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### SCREENING, COMPREHENSIVE BIOMARKER TESTING, DIAGNOSIS AND STAGING

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#### [Patterns and Factors Associated With Adherence to Lung Cancer Screening in Diverse Practice Settings](#) JAMA Netw Open. 2021 Apr 1;4(4):e218559. doi: 10.1001/jamanetworkopen.2021.8559.

Lori C Sakoda<sup>1, 2</sup>, M Patricia Rivera<sup>3, 4</sup>, et al.

**IMPORTANCE:** For lung cancer screening to confer mortality benefit, adherence to annual screening with low-dose computed tomography scans is essential. Although the National Lung Screening Trial had an adherence rate of 95%, current data are limited on screening adherence across diverse practice settings in the United States. **OBJECTIVE:** To evaluate patterns and factors associated with adherence to annual screening for lung cancer after negative results of a baseline examination, particularly in centralized vs decentralized screening programs. **DESIGN, SETTING, AND PARTICIPANTS:** This observational cohort study was conducted at 5 academic and community-based sites in North Carolina and California among 2283 individuals screened for lung cancer between July 1, 2014, and March 31, 2018, who met US Preventive Services Task Force eligibility criteria, had negative results of a baseline screening examination (American College of Radiology Lung Imaging Reporting and Data System category 1 or 2), and were eligible to return for a screening examination in 12 months. **EXPOSURES:** To identify factors associated with adherence, the association of adherence with selected baseline demographic and clinical characteristics, including type of screening program, was estimated using multivariable logistic regression. Screening program type was classified as centralized if individuals were referred through a lung cancer screening clinic or program and as decentralized if individuals had a direct clinician referral for the baseline low-dose computed tomography scan. **MAIN OUTCOMES AND MEASURES:** Adherence to annual lung cancer screening, defined as a second low-dose computed tomography scan within 11 to 15 months after baseline screening. **RESULTS:** Among the 2283 eligible individuals (1294 men [56.7%]; mean [SD] age, 64.9 [5.8] years; 1160 [50.8%] aged  $\geq 65$  years) who had negative screening results at baseline, overall adherence was 40.2% (n = 917), with higher adherence among those who underwent screening through centralized (46.0% [478 of 1039]) vs decentralized (35.3% [439 of 1244]) programs. The independent factor most strongly associated with adherence was type of screening program, with a 2.8-fold increased likelihood of adherence associated with centralized screening (adjusted odds ratio [aOR], 2.78; 95% CI, 1.99-3.88). Another associated factor was age (65-69 vs 55-59 years: aOR, 1.38; 95% CI, 1.07-1.77; 70-74 vs 55-59 years: aOR, 1.47; 95% CI, 1.10-1.96). **CONCLUSIONS**

**AND RELEVANCE:** After negative results of a baseline examination, adherence to annual lung cancer screening was suboptimal, although adherence was higher among individuals who were screened through a centralized program. These results support the value of centralized screening programs and the need to further implement strategies that improve adherence to annual screening for lung cancer.

[Adherence to National Comprehensive Cancer Network ALK Testing Guidelines for Patients with Advanced Non-Small Cell Lung Cancer in U.S. Community Medical Centers](#) Oncologist. 2021 Apr 6. doi: 10.1002/onco.13779. Online ahead of print.

**BACKGROUND:** National Comprehensive Cancer Network (NCCN) guidelines recommend biomarker testing as the first step in the management of patients with advanced non-small cell lung cancer (aNSCLC). We assessed anaplastic lymphoma kinase (ALK) testing rates and factors related to underuse in community medical systems between 2012 and 2019 to understand guideline adoption.

**METHODS:** A retrospective observational study using a nationwide electronic health record (EHR)-derived deidentified database was conducted. Patients with aNSCLC diagnosed in community medical centers from January 2012 to May 2019 were included to describe the ALK testing trend. This cohort was further restricted to patients diagnosed after 2015 to understand factors associated with testing underuse using mixed-effects multivariable logistic regression models. **RESULTS:** Trends for increased ALK testing rates by year were observed in both NCCN guideline-eligible patients (59.5% in 2012 to 84.1% in 2019) and -ineligible patients (15.6% to 50.8%) in a cohort of 41,728 patients. Histology type and smoking status had the greatest impact on test use. Compared with patients with nonsquamous histology and no smoking history, patients with squamous histology and no smoking history (adjusted odds ratio [aOR], 7.6; 95% confidence interval [CI], 5.6-10.4), NSCLC histology not otherwise specified (NOS) with smoking history (aOR, 3.4; 95% CI, 2.8-4.2); NSCLC NOS/nonsmoker (aOR, 1.8; 95% CI, 1.1-3.2), and nonsquamous/smoker (aOR, 1.5; 95% CI, 1.3-1.7) were less likely to be tested. Factors related to underuse also included Eastern Cooperative Oncology Group performance status, stage at initial diagnosis, and demographics. **CONCLUSION:** This analysis of real-world data shows increasing test use by year; however, one fifth of patients eligible for ALK testing still remain untested and potentially missing therapeutic options. **IMPLICATIONS FOR PRACTICE:** Advancement in treatment of lung cancer is accompanied by an increasing number of tests that should be run to determine potential therapy options for each patient. This study assessed adoption of testing recommendations for anaplastic lymphoma kinase rearrangements in a national database. Although test use increased over the time period studied (2012-2019), there is still room for improvement. Efforts are needed to increase test use in undertested groups, thus enabling eligible patients to benefit from novel lung cancer therapies.

[Healthcare Access, Utilization, and Preventive Health Behaviors by Eligibility for Lung Cancer Screening](#) J Cancer Educ. 2021 Apr;36(2):330-337. doi: 10.1007/s13187-019-01634-y.

Eric A Miller 1 , Paul F Pinsky 2

In 2013, the US Preventive Services Task Force recommended low-dose computed tomography screening for smokers at high risk of lung cancer; however, use remains low. Efforts to promote lung cancer screening need to consider how receptive this population is to preventive healthcare and cancer screening. In addition, because of demonstrated heterogeneity in behaviors by smoking status, interventions may need to differ among eligible high-risk subgroups. To assess the engagement of high-risk smokers in other preventive healthcare behaviors, we examined healthcare use, including non-lung cancer screening, and healthcare provider discussions regarding screening by eligibility for lung cancer screening. We used the 2015 National Health Interview Survey to assess smoking history, healthcare use, cancer screening, vaccinations, and healthcare provider discussions regarding non-lung cancer screening. We calculated weighted prevalence estimates and prevalence ratios comparing eligible and ineligible current and former smokers to never smokers. Eligible current and former smokers had significantly different healthcare

utilization and screening concordance compared to never smokers and to each other. Compared to never smokers, eligible current smokers were significantly less likely to be concordant with breast, colorectal, and cervical cancer screening while eligible former smokers were only less likely to be concordant with breast cancer screening. Eligible current smokers were less likely to report physician discussions about non-lung screening tests. Provider discussions about screening and engagement in preventive healthcare differed among current and former smokers eligible for lung cancer screening. Intervention efforts to increase lung cancer screening levels will likely need to differ as well.

[Video-Based Education in Lung Cancer Screening](#) J Cancer Educ. 2021 Apr;36(2):305-309. doi: 10.1007/s13187-019-01629-9. Juan Alban 1 , Luis-Felipe Alban 2 , Andrew Clayburn 3 , Amit Khanal 4 , Lawrence Feldman 5

Lung cancer (LC) is the leading cause of cancer mortality in the USA; the American Cancer Society (ACS) estimates upwards of 220,000 new cases will be diagnosed this year. Recently, the Center for Medicare/Medicaid Services (CMS) agreed to cover LC screening with low-dose computed tomography (CT) for patients; however, CMS requires prior documentation of a shared decision-making (SDM) visit between the patient and the referring clinician to inform them about risks of screening. LC screening programs have begun to use YouTube for patient recruitment, education, and marketing of screening. The objective of this study is to shed light on the role of YouTube in lung cancer screening in terms of guidelines, screening options, target population, steps after screening, and risks and benefits of screening. We searched YouTube.com™ to identify videos dealing with lung screening using the keywords: lung cancer screening. Videos without sound, uploaded before 2009, longer than 20 min, duplicate videos, and videos in a language other than English were excluded. This method yielded 123 videos that fit criteria. Videos were coded for inclusion of LC screening process, risks and benefits of screening, screening guidelines, risk factors for LC, and treatment options after LC diagnosis. One hundred twenty-three videos had a cumulative 261,261 views across all videos. A total of 38.7% of the videos included no mention of United States Preventive Services Task Force (USPSTF) or CMS guidelines for LC screening. Only 30% included any mention of the risks associated with screening: 14% mentioned false positives, 12% radiation, and 4% anxiety associated with screening. Ninety-two percent of all videos sampled were intended for patients, and the majority of videos were created by medical institutions (66%) and news channels (17%). Lung cancer screening videos on YouTube's platform have garnered a substantial amount of views. While all videos sampled highlighted the benefits of LC screening, the majority fail to discuss the risks associated with the screening process. Most videos were produced for marketing purposes rather than educational and therefore should not be used as a substitute for SDM visits.

[A Comparison of Web-Based Cancer Risk Calculators That Inform Shared Decision-making for Lung Cancer Screening](#) J Gen Intern Med. 2021 Apr 9. doi: 10.1007/s11606-021-06754-0. Online ahead of print. Frederick R Kates 1 , Ryan Romero 2 , Daniel Jones 3 , Jacqueline Egelfeld 4 , Santanu Datta 5

**INTRODUCTION:** To align patient preferences and understanding with harm-benefit perception, the Centers for Medicare & Medicaid Services (CMS) mandates that providers engage patients in a collaborative shared decision-making (SDM) visit before LDCT. Nonetheless, patients and providers often turn instead to the web for help making decisions. Several web-based lung cancer risk calculators (LCRCs) provide risk predictions and screening recommendations; however, the accuracy, consistency, and subsequent user interpretation of these predictions between LCRCs is ambiguous. We conducted a systematic review to assess this variability. **DESIGN:** Through a systematic Internet search, we identified 10 publicly available LCRCs and categorized their input variables: demographic factors, cancer history, smoking status, and personal/environmental factors. To assess variance in LCRC risk prediction outputs, we developed 16 hypothetical patients along a risk continuum, illustrated by randomly assigned input variables, and individually compared them to each LCRC against the empirically validated "gold-

standard" PLCO risk model in order to evaluate the accuracy of the LCRCs within identical time-windows. **RESULTS:** From the inclusion criteria, 11 calculators were initially identified. The analyzed calculators also vary in output characteristics and risk depiction for hypothetical patients. There were 13 total instances across ten hypothetical patients in which the sample standard error exceeded the mean risk percentage across all general samples and set standard calculations. The largest measured difference is 16.49% for patient 8, and the smallest difference is 0.01% for patient 2. The largest measured difference is 16.49% for patient 8, and the smallest difference is 0.01% for patient 2. **CONCLUSION:** Substantial variability in the depiction of lung cancer risk for hypothetical patients exists across the web-based LCRCs due to their respective inputs and risk prediction models. To foster informed decision-making in the SDM-LDCT context, the input variables, risk prediction models, risk depiction, and screening recommendations must be standardized to best practice.

**[Propensity-score-matching analysis to compare efficacy and safety between 16-gauge and 18-gauge needle in ultrasound-guided biopsy for peripheral pulmonary lesions](#)** BMC Cancer. 2021 Apr 9;21(1):390. doi: 10.1186/s12885-021-08126-7. Weijun Huang # 1 2 , Jieyi Ye # 2 , Yide Qiu 2 , Weiwei Peng 2 , Ninghui Lan 2 , Weizhen Cui 2 , Ting Huang 2 , Yinghui Ou 2 , Yingjia Li 3

**BACKGROUND:** Definitive diagnosis of peripheral pulmonary lesions (PPLs) depends on the histological analysis of the pleural biopsy sample. Ultrasound (US)-guided sampling is now standard practice in the clinical setting. However, determining a suitable needle size and sampling times to improve the efficacy and safety of the biopsy remains challenging. Here, we compared the efficacy between 16- and 18-gauge core biopsy needles in US-guided percutaneous transthoracic biopsy for PPLs on histological diagnosis and procedure-related complications. **MATERIALS AND METHODS:** In total, 1169 patients (767 men, 402 women; mean age,  $59.4 \pm 13.2$  years) who received biopsy for PPLs between September 2011 and February 2019 were included. The propensity score matching (PSM) analysis was performed to adjust the baseline differences, and the rate of successful specimen assessment and complications were compared between the 16-gauge (249 patients) and 18-gauge (920 patients) groups. The number of pleural surfaces crossed (NOPSC) was defined as the number of times the visceral pleural surface was transgressed. Stratified analysis was performed based on NOPSC. **RESULTS:** The overall success rate was 92.0% (1076/1169). The overall complication rate was 9.6%, including pneumothorax, hemorrhage, and vasovagal reaction, which occurred in 2.5% (29/1169), 6.6% (77/1169), and 0.5% (6/1169) of the patients, respectively. When NOPSC was 1 or  $> 2$ , the success and complication rates in the 16-gauge group were comparable to those of the 18-gauge group (all  $P > 0.05$ ). When the NOPSC was 2, the success rate in the 16-gauge group was significantly higher than that in the 18-gauge group ( $P = 0.017$ ), whereas the complication rate was comparable ( $P > 0.05$ ). **CONCLUSION:** Higher success rate could be achieved using a 16-gauge than an 18-gauge core biopsy needle in the US-guided percutaneous transthoracic biopsy for PPLs when the NOPSC was 2. We recommend using 16-gauge needles with 2 times of needle passes in biopsy for PPLs in clinical practice.

**[Patient Adherence in an Academic Medical Center's Low-dose Computed Tomography Screening Program](#)** Am J Clin Oncol. 2021 Apr 1. doi: 10.1097/COC.0000000000000817. Online ahead of print.

Keith D Mortman 1 , Joseph Devlin, Brian Giang, Ryan Mortman, Andrew D Sparks, Michael A Napolitano

**OBJECTIVES:** Low-dose computed tomography (LDCT) screening is an important tool for reducing lung cancer mortality. This study describes a single center's experience with LDCT and attempts to identify any barriers to compliance with standard guidelines. **MATERIALS AND METHODS:** This is a retrospective review of a single university-based hospital system from 2015 to 2019. All individuals who met eligibility for lung cancer screening were entered into a database. The definition of adherence with the screening program was determined by the recommended timeline for the follow-up LDCT. Cohorts

were split by adherence and demographics were compared. **RESULTS:** A total of 203 LDCTs were performed in 121 patients who met eligibility for LDCT and had appropriate surveillance from 2015 to 2019. The average age was 64 years old. The overall adherence rate for prescribed LDCTs was 59.1%. Patients with Lung-RADS score 2 had 2.43 times higher odds of adherence relative to patients with Lung-RADS score 1 (odds ratio [OR]=2.43; 95% confidence interval [CI]: 1.23-4.83; P=0.011). African American patients had 42% lower odds of adherence relative to white patients (OR=0.58; 95% CI: 0.32-1.06; P=0.076). Patients with non-District of Columbia zip codes had 57% higher odds of adherence relative to those with District of Columbia zip codes, although this did not reach statistical significance (OR=1.57; 95% CI: 0.87-2.82; P=0.136). **CONCLUSIONS:** Despite the implementation of a multidisciplinary, academic LDCT screening program, overall adherence rate to prescribed follow-up scans was suboptimal. Socioeconomic disparities and African American race may negatively affect adherence to lung cancer screening LDCT guidelines. Patients with concerning findings on initial LDCT had a higher association of adherence to guidelines.

[Molecular Biomarker and Program Death-Ligand 1 Expression Testing in Patients with Advanced Stage Non-Small Cell Lung Cancer Across North Carolina Community Hospitals](#) Chest. 2021 Apr 19;S0012-3692(21)00702-9. doi: 10.1016/j.chest.2021.04.014. Online ahead of print. M Patricia Rivera 1 , Marjory Charlot 2 , Danielle D Durham 3 , et al.

**BACKGROUND:** Precision medicine in advanced non-small cell lung cancer (NSCLC) requires molecular biomarker testing in patients with non-squamous and select patients with squamous histologies, and PD-L1 testing in both. **RESEARCH QUESTION:** What are rates of molecular and PD-L1 biomarker testing in patients with advanced NSCLC in community practices and do rates vary by sociodemographic factors? What is the prevalence of molecular biomarker mutations and PD-L1 expression levels? **STUDY DESIGN AND METHODS:** From 389 stage IV NSCLC pathology reports obtained through the UNC Lineberger Comprehensive Cancer Center's Rapid Case Ascertainment Program from 38 community hospitals across North Carolina, we abstracted demographics, histology, molecular biomarker testing and results, PD-L1 testing and expression. We geocoded patient and hospital addresses to determine travel time, distance to care, and census block level contextual variables. We compared molecular biomarker and PD-L1 testing rates, the prevalence of molecular biomarkers, and PD-L1 expression levels by race and sex using chi-square tests. We determined predictors of testing using multivariable logistic regression and report adjusted odds ratios (aOR) and 95% confidence intervals (95% CI). **RESULTS:** Among patients with non-squamous NSCLC, 64.4% were tested for molecular biomarkers and among all NSCLC patients 53.2% were tested for PD-L1 expression. Differences in biomarker testing rates by sociodemographic factors were not statistically significant in univariate or adjusted analyses. Adjusted analyses showed patients living in areas with higher household internet access were more likely to undergo PD-L1 testing (aOR=1.66, 95% CI:1.02-2.71). Sociodemographic differences in molecular biomarker prevalence and PD-L1 expression levels were not statistically significant, except for HER2 mutations which occurred in 16.7% of males vs. 0% in females, p=0.05. **INTERPRETATION:** Biomarker testing remains underutilized in NSCLC. Future work should include larger populations and evaluate hospital-specific testing protocols to identify and address barriers to guideline-recommended testing.

[Predicting Lymph Node Metastasis in Non-Small Cell Lung Cancer: Prospective External and Temporal Validation of the HAL and HOMER Models](#) Chest. 2021 Apr 28;S0012-3692(21)00856-4. doi: 10.1016/j.chest.2021.04.048. Online ahead of print. Gabriela Martinez-Zayas 1 , Francisco A Almeida 2 , Lonny Yarmus 3 , et al.

**BACKGROUND:** Two models, the Help with the Assessment of Adenopathy in Lung cancer (HAL) and Help with Oncologic Mediastinal Evaluation for Radiation (HOMER), were recently developed to

estimate the probability of nodal disease in non-small cell lung cancer (NSCLC) patients as determined by endobronchial ultrasound-transbronchial needle aspiration (EBUS-TBNA). The objective of this study was to prospectively externally validate both models at multiple centers. **RESEARCH QUESTION:** Are the HAL and HOMER models valid across multiple centers? **STUDY DESIGN AND METHODS:** This multicenter prospective observational cohort study enrolled consecutive patients with PET-CT clinical-radiographic stage T1-3, N0-3, M0 NSCLC undergoing EBUS-TBNA staging. HOMER was used to predict the probability of N0 vs. N1 vs. N2 or N3 (N2|3) disease and HAL was used to predict the probability of N2|3 (vs N0 or N1) disease. Model discrimination was assessed using the area under the receiver operating characteristics curve (ROC-AUC) while calibration was assessed using the Brier score, calibration plots, and the Hosmer-Lemeshow test. **RESULTS:** Thirteen centers enrolled 1,799 patients. HAL and HOMER demonstrated good discrimination: HAL ROC-AUC=0.873 (95%CI 0.856-0.891) and HOMER ROC-AUC=0.837 (95%CI 0.814-0.859) for predicting N1 disease or higher (N1|2|3) and 0.876 (95%CI 0.855-0.897) for predicting N2|3 disease. Brier scores were 0.117 and 0.349 respectively. Calibration plots demonstrated good calibration for both models. For HAL the difference between forecast and observed probability of N2|3 disease was +0.012; for HOMER the difference for N1|2|3 was -0.018 and for N2|3 was +0.002. The Hosmer-Lemeshow test was significant for both models ( $p=0.034$  and  $0.002$ ) indicating a small but statistically significant calibration error. **INTERPRETATION:** HAL and HOMER demonstrated good discrimination and calibration in multiple centers. Although calibration error was present, the magnitude of the error is small, such that the models are informative.

#### [A Retrospective Multi-Site Academic Center Analysis of Pneumothorax and Associated Risk Factors after CT-Guided Percutaneous Lung Biopsy](#)

Lung. 2021 Apr 19. doi: 10.1007/s00408-021-00445-7. Online ahead of print. Esther Rong 1, David A Hirschl 2, Benjamin Zalta 2, Anna Shmukler 2 3, Steven Krausz 2, Jeffrey M Levsky 2, Juan Lin 4, Linda B Haramati 2, Arash Gohari 2  
**PURPOSE:** To assess the risk factors, incidence and significance of pneumothorax in patients undergoing CT-guided lung biopsy. **METHODS:** Patients who underwent a CT-guided lung biopsy between August 10, 2010 and September 19, 2016 were retrospectively identified. Imaging was assessed for immediate and delayed pneumothorax. Records were reviewed for presence of risk factors and the frequency of complications requiring chest tube placement. 604 patients were identified. Patients who underwent chest wall biopsy (39) or had incomplete data (9) were excluded. **RESULTS:** Of 556 patients (average age 66 years, 50.2% women) 26.3% (146/556) had an immediate pneumothorax and 2.7% (15/556) required chest tube placement. 297/410 patients without pneumothorax had a delayed chest X-ray. Pneumothorax developed in 1% (3/297); one patient required chest tube placement. Pneumothorax risk was associated with smaller lesion sizes (OR 0.998; 95% CI (0.997, 0.999); [ $p = 0.002$ ]) and longer intrapulmonary needle traversal (OR 1.055; 95% CI (1.033, 1.077); [ $p < 0.001$ ]). Previous ipsilateral lung surgery (OR 0.12; 95% CI (0.031, 0.468); [ $p = 0.002$ ]) and longer needle traversal through subcutaneous tissue (OR 0.976; 95% CI (0.96, 0.992); [ $p = 0.0034$ ]) were protective of pneumothorax. History of lung cancer, biopsy technique, and smoking history were not significantly associated with pneumothorax risk. **CONCLUSION:** Delayed pneumothorax after CT-guided lung biopsy is rare, developing in 1% of our cohort. Pneumothorax is associated with smaller lesion size and longer intrapulmonary needle traversal. Previous ipsilateral lung surgery and longer needle traversal through subcutaneous tissues are protective of pneumothorax. Stratifying patients based on pneumothorax risk may safely obviate standard post-biopsy delayed chest radiographs.

#### [Augmented Fluoroscopy: A New and Novel Navigation Platform for Peripheral Bronchoscopy](#)

J Bronchology Interv Pulmonol. 2021 Apr 1;28(2):116-123. doi: 10.1097/LBR.0000000000000722. Joseph Cicenya 1, Krish Bhadra 2, Sonali Sethi 1, Daniel A Nader 3, Patrick Whitten 4, Douglas Kyle Hogarth 5

**BACKGROUND:** The diagnosis of lung nodules continues to be a challenge. Confirmed diagnosis allows appropriate treatment for cancers and allows avoidance of more invasive procedures for proven noncancers. Currently, available lung biopsy technologies each have their own limitations, which affect the ability to successfully navigate to a suspicious nodule and to collect a diagnostic sample. Additional advancements in endobronchial navigation, localization, and guided biopsy are needed to obtain higher rates of definitive diagnosis for lung nodules. **METHODS:** This is a prospective, multicenter study that assessed the localization success rate and diagnostic yield of bronchoscopies guided only by the LungVision platform. Physicians navigated to pulmonary nodules according to a proposed pathway and verified nodule location using radial endobronchial ultrasound before the biopsy. **RESULTS:** Fifty-five patients were enrolled in the study. Two patients had >1 nodule that was evaluated on the day of the procedure. During bronchoscopy, the nodule localization success rate was 93%. The overall diagnostic yield measured the day of the procedure, based on the immediate rapid on-site pathology report, was 75.4%. **CONCLUSION:** LungVision provides reliable navigation and ability to biopsy pulmonary nodules with an acceptable success rate. The platform demonstrates a high localization rate of pulmonary nodules.

[EBUS-TBNA Cytological Samples for Comprehensive Molecular Testing in Non-Small Cell Lung Cancer](#) Cancers (Basel). 2021 Apr 25;13(9):2084. doi: 10.3390/cancers13092084. Roberto Martin-Deleon 1 , Cristina Teixido 2 3 , et al.

Clinical guidelines promote the identification of several targetable biomarkers to drive treatment decisions in advanced non-small cell lung cancer (NSCLC), but half of all patients do not have a viable biopsy. Specimens from endobronchial-ultrasound transbronchial needle aspiration (EBUS-TBNA) are an alternative source of material for the initial diagnosis of NSCLC, however their usefulness for a complete molecular characterization remains controversial. EBUS-TBNA samples were prospectively tested for several biomarkers by next-generation sequencing (NGS), nCounter, and immunohistochemistry (PD-L1). The primary objectives were to assess the sensitivity of EBUS-TBNA samples for a comprehensive molecular characterization and to compare its performance to the reference standard of biopsy samples. Seventy-two EBUS-TBNA procedures were performed, and 42 NSCLC patients were diagnosed. Among all cytological samples, 92.9% were successfully genotyped by NGS, 95.2% by nCounter, and 100% by immunohistochemistry. There were 29 paired biopsy samples; 79.3% samples had enough tumor material for genomic genotyping, and 96.6% for PD-L1 immunohistochemistry. A good concordance was found between both sources of material: 88.9% for PD-L1, 100% for NGS and nCounter. EBUS-TBNA is a feasible alternative source of material for NSCLC genotyping and allows the identification of patient candidates for personalized therapies with high concordance when compared with biopsy.

## CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES

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### NSCLC - SURGERY

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[Combination of nitrous oxide and the modified inflation-deflation method for identifying the intersegmental plane in segmentectomy: A randomized controlled trial](#) Thorac Cancer. 2021 May;12(9):1398-1406. doi: 10.1111/1759-7714.13919. Epub 2021 Apr 4. Wenjing Yang # 1 , Zicheng Liu # 2 , Chun Yang 1 , et al.

Shijiang Liu 1 , Minna Guo 1 , Wei Wen 2 , Jun Wang 2 , Cunming Liu 1 , Quan Zhu 2

**BACKGROUND:** During thoracoscopic segmentectomy, accurately and rapidly identifying the intersegmental plane (ISP) is of great importance. This study aimed to investigate the effect and safety of a nitrous oxide (N<sub>2</sub>O)/oxygen (O<sub>2</sub>) inspired mixture on the appearance time of the ISP (TISP) via the modified inflation-deflation method. **METHODS:** A total of 65 participants who underwent

segmentectomy were randomized into three groups: 75% N<sub>2</sub> O (n = 24), 50% N<sub>2</sub> O (n = 23) or 0% N<sub>2</sub> O (n = 18). The 75% N<sub>2</sub> O group received a gas mixture of N<sub>2</sub> O/O<sub>2</sub> (Fio<sub>2</sub> = 0.25), the 50% N<sub>2</sub> O group received N<sub>2</sub> O/O<sub>2</sub> (Fio<sub>2</sub> = 0.5), and the 0% N<sub>2</sub> O group received 100% oxygen during lung expansion. The appearance time of satisfactory and ideal planes was recorded. Furthermore, arterial blood gas at breathing room air, one-lung ventilation (OLV) before lung expansion, 5 and 15 min after lung expansion were also recorded. **RESULTS:** TISP was significantly shorter in the 75% N<sub>2</sub> O group (320.2 ± 65.9 s) compared with that of the 50% N<sub>2</sub> O group (552.4 ± 88.9 s, p < 0.001) and the 0% N<sub>2</sub> O group (968.3 ± 85.5 s, p < 0.001), while the 50% N<sub>2</sub> O group was shorter than that of the 0% N<sub>2</sub> O group (p < 0.001). Arterial oxygenation was significantly improved in the 0% N<sub>2</sub> O group only after lung expansion, before which there were no differences in mean PaO<sub>2</sub> values among groups. **CONCLUSIONS:** The use of N<sub>2</sub> O in the inspired gas mixture during lung expansion is an applicable strategy to rapidly identify the ISP via the modified inflation-deflation method without any adverse effect on OLV related arterial oxygenation during segmentectomy.

**Targeted Sequencing Analysis of Predominant Histological Subtypes in Resected Stage I Invasive Lung Adenocarcinoma** J Cancer. 2021 Apr 2;12(11):3222-3229. doi: 10.7150/jca.51405. eCollection 2021. Yan Li 1 2, Yan Tan 3, Song Hu 1, Jun Xie 1, Zhantao Yan 3, Xian Zhang 1, Yun Zong 1, Han Han-Zhang 4, Qing Li 3, Chong Li 1

**OBJECTIVE:** Lung adenocarcinoma (LADC) is classified into five main histological subtypes with distinct clinicopathologic characteristics: lepidic-predominant adenocarcinoma (LPA), acinar-predominant adenocarcinoma (APA), papillary-predominant adenocarcinoma (PPA), micropapillary-predominant adenocarcinoma (MPA) and solid-predominant adenocarcinoma (SPA). However, the mutational profiles of predominant histological subtypes have not been well defined. In this study, we aimed to reveal the genomic landscape of 5 main histological subtypes. **PATIENTS AND METHODS:** We performed next-generation sequencing (NGS) in a cohort of 86 stage I invasive adenocarcinoma (IAC) patients, using a customized panel including 168 cancer-associated genes. **RESULTS:** Our analysis identified a total of 302 genomic alterations. Five subtypes showed different mutation profiles with LPA, APA, PPA, MPA and SPA had an average mutation rate of 1.95 (range: 0-5), 2.56 (range: 1-6), 3.5 (range: 1-7), 3.75 (range: 1-8) and 6.05 (range: 2-12), respectively (p=4.17e-06). Driver mutations occurred in 96.55% (83/86) of all patients. EGFR (73.3%), KRAS (9.3%), ALK (4.7%) and MET (4.7%) are the most commonly mutated lung cancer driver genes, TP53 is the top mutated tumor suppressor gene. SPA patients harbored more driver mutations and higher frequency of TP53 than LPA patients. Interestingly, LRP1B mutations, which has been reported to be associated with high tumor mutation burden and better response to immunotherapy, were only detected from 5 SPA patients (p=0.001). No patients from other four cohorts harbored LRP1B mutations. **CONCLUSIONS:** We revealed distinctive mutation landscape of the 5 major histological subtypes of LADC, evident by distinctive average mutation rate with SPA and LPA having the highest and lowest average mutation rate, respectively. SPA patients showed higher mutation rate of LRP1B and higher rates for PD-L1 positivity, indicating that SPA patients may have better response to immunotherapy.

**Impact of the Extent of Lymph Node Dissection on Precise Staging and Survival in Clinical I-II Pure-Solid Lung Cancer Undergoing Lobectomy** J Natl Compr Canc Netw. 2021 Jan 28;19(4):393-402. doi: 10.6004/jnccn.2020.7635. Print 2021 Apr. Donglai Chen 1, Yiming Mao 2, Junmiao Wen 3 4, et al.

**BACKGROUND:** This study sought to determine the optimal number of examined lymph nodes (ELNs) and examined node stations (ENSs) in patients with radiologically pure-solid non-small cell lung cancer (NSCLC) who underwent lobectomy and ipsilateral lymphadenectomy by investigating the impact of ELNs and ENSs on accurate staging and long-term survival. **MATERIALS AND METHODS:** Data



from 6 institutions in China on resected clinical stage I-II (cI-II) NSCLCs presenting as pure-solid tumors were analyzed for the impact of ELNs and ENSs on nodal upstaging, stage migration, recurrence-free survival (RFS), and overall survival (OS). Correlations between different endpoints and ELNs or ENSs were fitted with a LOWESS smoother, and the structural break points were determined by Chow test. **RESULTS:** Both ELNs and ENSs were identified as independent prognostic factors for OS (ENS hazard ratio [HR], 0.690; 95% CI, 0.597-0.797; P<.001; ELN HR, 0.950; 95% CI, 0.917-0.983; P=.004) and RFS (ENS HR, 0.859; 95% CI, 0.793-0.931; P<.001; ELN HR, 0.960; 95% CI, 0.942-0.962; P<.001), which were also associated with postoperative nodal upstaging (ENS odds ratio [OR], 1.057; 95% CI, 1.002-1.187; P=.004; ELN OR, 1.186; 95% CI, 1.148-1.226; P<.001). A greater number of ELNs and ENSs correlated with a higher accuracy of nodal staging and a lower probability of stage migration. Cut-point analysis revealed an optimal cutoff of 18 LNs and 6 node stations for stage cI-II pure-solid NSCLCs, which were validated in our multi-institutional cohort. **CONCLUSIONS:** Extensive examination of LNs and node stations seemed crucial to predicting accurate staging and survival outcomes. A threshold of 18 LNs and 6 node stations might be considered for evaluating the quality of LN examination in patients with stage cI-II radiologically pure-solid NSCLCs.

**Redefining the Risk of Surgery for Clinical Stage IIIA (N2) Non-Small Cell Lung Cancer: A Pooled Analysis of the STS GTSD and ESTS Registry** Lung. 2021 Apr 28. doi: 10.1007/s00408-021-00447-5.

Online ahead of print. Andrew T Arndt 1 , Alessandro Brunelli 2 , Silvia Cicconi 3 , et al.

**BACKGROUND:** Management of clinical stage IIIA-N2 (cIIIA-N2) non-small cell lung cancer (NSCLC) remains controversial. We evaluated treatment strategies and outcomes in cIIIA-N2 NSCLC patients who underwent pulmonary resection in The Society of Thoracic Surgeons General Thoracic Surgery Database (STS GTSD) and the European Society of Thoracic Surgeons (ESTS) Registry.

**METHODS:** The STS GTSD and ESTS Registry were queried for patients who underwent pulmonary resection for cIIIA-N2 NSCLC between 2012 and 2016. Demographic variables, treatment strategies, and outcome measures were collected and analyzed. Significance of differences was determined using the  $\chi^2$  test for categorical variables and the Wilcoxon rank sum test for continuous variables. **RESULTS:** Pulmonary resection was performed in 4279 cIIIA-N2 NSCLC patients (2928 STS GTSD; 1351 ESTS). Induction therapy was administered to 49%. Lobectomy was performed in 67.1% and pneumonectomy in 13%. Lobectomy was associated with 19.2% major morbidity and 1.6% operative mortality, while pneumonectomy was associated with 34.1% and 5%, respectively. Induction therapy was associated with a higher rate of major morbidity or mortality than upfront surgery (23.2% vs 19.5%, p = 0.004), driven by pneumonectomy (40.7% vs 30.3%, p = 0.012) rather than lobectomy (20.3% vs 18.8%, p = 0.31).

**CONCLUSIONS:** Pulmonary resection for cIIIA-N2 NSCLC is associated with low rates of operative morbidity and mortality, with lobectomy having lower morbidity and mortality than pneumonectomy. Induction therapy, particularly chemoradiotherapy, is associated with a higher rate of composite morbidity or mortality than upfront surgery in pneumonectomy patients but not lobectomy patients.

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

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**Poziotinib for EGFR and HER2 exon 20 insertion mutation in advanced NSCLC: Results from the expanded access program** Eur J Cancer. 2021 May;149:235-248. doi: 10.1016/j.ejca.2021.02.038. Epub 2021 Apr 2. Arselà Prelaj 1 , Achille Bottiglieri 2 , Claudia Proto 2 , et al.

2021 Apr 2. Arselà Prelaj 1 , Achille Bottiglieri 2 , Claudia Proto 2 , et al.

**BACKGROUND:** The treatment of metastatic non-small-cell lung cancer (mNSCLC) patients with EGFR/HER2 exon 20 insertion mutation (i-mut) remains an unmet clinical need. Poziotinib, a new generation tyrosine kinase inhibitor, is currently under investigation as a potential targeted therapy. This compassionate study of its use aims to describe the activity/toxicity of poziotinib in mNSCLC with EGFR/HER2-exon-20-i-mut. **PATIENTS AND METHODS:** NSCLC patients who were treated either

with EGFR or HER2 exon 20-i-mut within an expanded access program were included in this study. Poziotinib (16 mg or less) was administered orally quaque die (QD). The primary end-point was the overall response rate (ORR) assessed by central review using RECIST v1.1, and secondary end-points were median progression free survival (PFS), disease control rate (DCR), median overall survival (OS) and toxicity. **RESULTS:** The median age of all the 30 patients was 58 years (25-80 years), most of them were females (73%); ECOG 0-1 (83%), EGFR i-mut (73%) and pre-treated (83%). 73% started with poziotinib at a dose of 16 mg. At data cut-off, 22 of 33 patients (73%) experienced a progress in the disease and 12 of 30 (40%) died. Median PFS was 5.6 months (95% CI: 3.6-6.7 months) and the mOS 9.5 months (95% CI: 5.3 - not-reached months). The ORR was 30% (EGFR/HER2: 23/50%) and DCR 80%. G3 AEs were reported in 66% of the patients and were found with skin rash (50%), diarrhoea (17.6%), mucositis (7%) and paronychia (3%). G5, possibly associated with pneumonitis might also have occurred. **CONCLUSIONS:** Poziotinib exhibited effects in mNSCLC patients with EGFR/HER2-exon 20-i-mut. The toxicity rate was high leading to frequent dose interruption and reduction, thereby reducing mPFS in patients with good ORR/DCR. ZENITH20 trial is now being used to evaluate the low dose and new scheduled dose (e.g. bis in die (BIS)).

### **Safety and Efficacy of First-Line Pembrolizumab in Black Patients with Metastatic Non-Small Cell Lung Cancer**

Oncologist. 2021 Apr 12. doi: 10.1002/onco.13787. Online ahead of print. Monica Peravali 1 , Jaecil Ahn 2 , Kevin Chen 3 , Suman Rao 3 , Irina Veytsman 1 , Stephen V Liu 4 , Chul Kim 4  
**INTRODUCTION:** Pembrolizumab, an immune checkpoint inhibitor (ICI), has become an integral part of front-line treatment of metastatic non-small cell lung cancer (NSCLC). However, pivotal trials had significant underrepresentation of Black patients (pts). Lack of sufficient evidence regarding safety and efficacy of ICIs among minority racial groups poses a challenge in delivery of optimal cancer directed care. **METHODS:** We retrospectively reviewed pts with stage IV NSCLC treated with first-line pembrolizumab across three MedStar facilities between January 1, 2014, and May 3, 2019. Progression-free survival (PFS) and overall survival (OS) were primary endpoints and were calculated using the Kaplan-Meier method. Immune-related adverse events (irAEs) were assessed according to Common Terminology Criteria for Adverse Events Version 5.0 (CTCAE v5.0). **RESULTS:** In total, 136 pts were identified, with 74 (54.4%) White, 53 (39%) Black, 2 (1.5%) Asian, and 7 (5.1%) other racial groups. Median age was 70 years in White pts and 65 years in Black pts ( $p < .01$ ). There was no difference in median PFS (5.7 vs. 5.9 months;  $p = .651$ ) or OS (11.8 vs. 12.4 months;  $p = .949$ ) between White and Black pts. In the subset of patients whose tumors had high programmed death-ligand 1 (PD-L1) expression ( $\geq 50\%$ ), there was still no difference in efficacy by race. Median PFS (8.7 vs. 3.9 months;  $p = .843$ ) and OS (14.7 vs. 11.3 months;  $p = .581$ ) in White versus Black pts were not different. Incidence of irAEs in White versus Black pts was 24.3% and 22.6%, respectively ( $p = .83$ ). **CONCLUSION:** We found no major differences in either safety or efficacy of first-line pembrolizumab between White and Black pts. Use of first-line pembrolizumab-based treatment in Black pts with stage IV NSCLC is safe and efficacious, based on these real-world data. **IMPLICATIONS FOR PRACTICE:** Immunotherapy has revolutionized treatment of solid and hematological malignancies. There are certain populations of patients underrepresented in the original trials including minority racial groups, patients with autoimmune diseases, and those with chronic viral illnesses. Our study focuses on Black patients with metastatic lung cancer who received pembrolizumab and concludes similar safety and response to treatment when compared with White patients. Black patients are an important demographic group in clinical practice often facing systemic health care disparities. This study paves a path for future studies in underrepresented populations receiving immunotherapy across various malignancies.D)).

[A Phase Ib/II Study of Pepinemab in Combination with Avelumab in Advanced Non-Small Cell Lung Cancer](#) Clin Cancer Res. 2021 Apr 5. doi: 10.1158/1078-0432.CCR-20-4792. Online ahead of print. Michael R Shafique 1, Terrence L Fisher 2, Elizabeth E Evans 3, et al.

**PURPOSE:** The CLASSICAL-Lung clinical trial tested the combination of pepinemab, an IgG4 humanized mAb targeting semaphorin 4D, with the PD-L1 inhibitor avelumab to assess the effects of coupling increased T-cell infiltration and reversal of immune suppression via pepinemab with sustained T-cell activation via checkpoint inhibition. **PATIENTS AND METHODS:** This phase Ib/II, single-arm study was designed to evaluate the safety, tolerability, and efficacy of pepinemab in combination with avelumab in 62 patients with advanced non-small cell lung cancer (NSCLC), including immunotherapy-naïve (ION) patients and patients whose tumors progressed following anti-PD-1/L1 monotherapy (IOF). The main objectives were to evaluate safety/tolerability, establish a recommended phase 2 dose (RP2D), obtain a preliminary evaluation of antitumor activity, and investigate candidate biomarker activity.

**RESULTS:** The combination was well tolerated with no major safety signals identified. Pepinemab, 10 mg/kg with avelumab, 10 mg/kg, every 2 weeks, was selected as the RP2D. Among 21 evaluable ION patients, 5 patients experienced partial responses (PR), 4 patients evidenced clinical benefit  $\geq 1$  year, and the disease control rate (DCR) was 81%. Notably, overall response rate with the combination therapy was higher than previously reported for single-agent avelumab in the PD-L1-negative/low population. Among 29 evaluable IOF patients, the combination resulted in a DCR of 59%, including 2 PR and 7 patients with durable clinical benefit of  $\geq 23$  weeks. Biomarker analysis of biopsies demonstrated increased CD8 T-cell density correlating with RECIST response criteria. **CONCLUSIONS:** The combination of pepinemab with avelumab was well tolerated in NSCLC and showed signs of antitumor activity in immunotherapy-resistant and PD-L1-negative/low tumors.

[Real-world outcomes of first-line pembrolizumab plus pemetrexed-carboplatin for metastatic nonsquamous NSCLC at US oncology practices](#) Sci Rep. 2021 Apr 28;11(1):9222. doi:

10.1038/s41598-021-88453-8. Vamsidhar Velcheti 1, Xiaohan Hu 2, Bilal Piperdi 2 3, Thomas Burke 2

Evidence from real-world clinical settings is lacking with regard to first-line immunotherapy plus chemotherapy for the treatment of non-small cell lung cancer (NSCLC). Our aim was to describe outcomes for patients treated with first-line pembrolizumab-combination therapy for metastatic nonsquamous NSCLC in US oncology practices. Using an anonymized, nationwide electronic health record-derived database, we identified patients who initiated pembrolizumab plus pemetrexed-carboplatin in the first-line setting (May 2017 to August 2018) after diagnosis of metastatic nonsquamous NSCLC that tested negative for EGFR and ALK genomic aberrations. Eligible patients had ECOG performance status of 0-1. An enhanced manual chart review was used to collect outcome information. Time-to-event analyses were performed using the Kaplan-Meier method. Of 283 eligible patients, 168 (59%) were male; median age was 66 years (range 33-84); and the proportions of patients with PD-L1 tumor proportion score (TPS) of  $\geq 50\%$ , 1-49%,  $< 1\%$ , and unknown were 28%, 27%, 28%, and 17%, respectively. At data cutoff on August 31, 2019, median patient follow-up was 20.3 months (range 12-28 months), and median real-world times on treatment (rwToT) with pembrolizumab and pemetrexed were 5.6 (95% CI 4.5-6.4) and 2.8 months (95% CI 2.2-3.5), respectively. Median overall survival (OS) was 16.5 months (95% CI 13.2-20.6); estimated 12-month survival was 59.5% (95% CI 53.3-65.0); rwProgression-free survival was 6.4 months (95% CI 5.4-7.8); and rwTumor response rate (complete or partial response) was 56.5% (95% CI 50.5-62.4). Median OS was 20.6, 16.3, 13.2, and 13.7 months for patient cohorts with PD-L1 TPS  $\geq 50\%$ , 1-49%,  $< 1\%$ , and unknown, respectively. These findings demonstrate the effectiveness of pembrolizumab plus pemetrexed-carboplatin by describing clinical outcomes among patients with metastatic nonsquamous NSCLC who were treated at US oncology practices.

[Five-Year Outcomes With Pembrolizumab Versus Chemotherapy for Metastatic Non-Small-Cell Lung Cancer With PD-L1 Tumor Proportion Score  \$\geq\$  50](#) J Clin Oncol. 2021 Apr 19;JCO2100174. doi: 10.1200/JCO.21.00174. Online ahead of print. Martin Reck <sup>1</sup>, Delvys Rodríguez-Abreu <sup>2</sup>, Andrew G Robinson <sup>3</sup>, et al.

**PURPOSE:** We report the first 5-year follow-up of any first-line phase III immunotherapy trial for non-small-cell lung cancer (NSCLC). KEYNOTE-024 (ClinicalTrials.gov identifier: NCT02142738) is an open-label, randomized controlled trial of pembrolizumab compared with platinum-based chemotherapy in patients with previously untreated NSCLC with a programmed death ligand-1 (PD-L1) tumor proportion score of at least 50% and no sensitizing EGFR or ALK alterations. Previous analyses showed pembrolizumab significantly improved progression-free survival and overall survival (OS). **METHODS:** Eligible patients were randomly assigned (1:1) to pembrolizumab (200 mg once every 3 weeks for up to 35 cycles) or platinum-based chemotherapy. Patients in the chemotherapy group with progressive disease could cross over to pembrolizumab. The primary end point was progression-free survival; OS was a secondary end point. **RESULTS:** Three hundred five patients were randomly assigned: 154 to pembrolizumab and 151 to chemotherapy. Median (range) time from randomization to data cutoff (June 1, 2020) was 59.9 (55.1-68.4) months. Among patients initially assigned to chemotherapy, 99 received subsequent anti-PD-1 or PD-L1 therapy, representing a 66.0% effective crossover rate. Median OS was 26.3 months (95% CI, 18.3-40.4) for pembrolizumab and 13.4 months (9.4-18.3) for chemotherapy (hazard ratio, 0.62; 95% CI, 0.48-0.81). Kaplan-Meier estimates of the 5-year OS rate were 31.9% for the pembrolizumab group and 16.3% for the chemotherapy group. Thirty-nine patients received 35 cycles (ie, approximately 2 years) of pembrolizumab, 82.1% of whom were still alive at data cutoff (approximately 5 years). Toxicity did not increase with longer treatment exposure. **CONCLUSION:** Pembrolizumab provides a durable, clinically meaningful long-term OS benefit versus chemotherapy as first-line therapy for metastatic NSCLC with PD-L1 tumor proportion score of at least 50%.

[Osimertinib versus osimertinib plus chemotherapy for non-small cell lung cancer with EGFR \(T790M\)-associated resistance to initial EGFR inhibitor treatment: An open-label, randomised phase 2 clinical trial](#) Eur J Cancer. 2021 May;149:14-22. doi: 10.1016/j.ejca.2021.02.019. Epub 2021 Apr 1. Kentaro Tanaka <sup>1</sup>, Hajime Asahina <sup>2</sup>, Junji Kishimoto <sup>3</sup>, et al.

**BACKGROUND:** Osimertinib is now a standard treatment for patients with previously untreated EGFR-mutated advanced non-small cell lung cancer (NSCLC). We here investigated whether the combination of osimertinib with cytotoxic chemotherapy might hold additive efficacy, as well as tolerability.

**PATIENTS AND METHODS:** We conducted an open-label randomised phase 2 study to evaluate osimertinib and carboplatin-pemetrexed combination in comparison with osimertinib monotherapy in EGFR mutation-positive NSCLC patients who experienced disease progression associated with the emergence of the T790M resistance mutation of EGFR during first-line EGFR-TKI therapy. The primary endpoint was PFS, with secondary endpoints, including OS, response, and safety. Given that osimertinib was approved as a first-line treatment during the study, patient accrual was discontinued, and a final analysis was performed for the 62 enrolled patients. **RESULTS:** Median PFS was 15.8 months for the osimertinib monotherapy group and 14.6 months for the combination therapy group (hazard ratio of 1.09, with a 95% confidence interval of 0.51-2.32; P = .83). Median OS was not reached in either group. The overall response rate was 71.4% in the osimertinib monotherapy group and 53.6% in the combination group. The frequency or severity of known adverse events in the combination group was comparable to those with carboplatin and pemetrexed previously reported, and novel adverse events were not observed in this study. **CONCLUSION:** This is the first randomised study to investigate the efficacy and safety of the combination of osimertinib and cytotoxic chemotherapy for EGFR-mutated NSCLC. The addition of chemotherapy to osimertinib as a second-line treatment did not prolong survival, while it was found to be generally tolerable. This combination strategy will be further validated in the first-line setting.

### [Pemetrexed Plus Platinum With or Without Pembrolizumab in Patients With Previously Untreated Metastatic Nonsquamous NSCLC: Protocol-Specified Final Analysis From KEYNOTE-189](#)

Ann Oncol. 2021 Apr 21;S0923-7534(21)01146-7. doi: 10.1016/j.annonc.2021.04.008. Online ahead of print. Authors Speranza 7 , F De Angelis 7 , M Dómine 8 , et al.

**BACKGROUND:** In the phase 3 KEYNOTE-189 study (NCT02578680), pembrolizumab plus pemetrexed and platinum-based chemotherapy (pemetrexed-platinum) significantly improved overall survival (OS) and progression-free survival (PFS) in patients with previously untreated metastatic nonsquamous NSCLC versus placebo plus pemetrexed-platinum. We report updated efficacy outcomes from the protocol-specified final analysis, including outcomes in patients who crossed over to pembrolizumab from pemetrexed-platinum and in patients who completed 35 cycles (approximately 2 years) of pembrolizumab. **PATIENTS AND METHODS:** Eligible patients were randomized 2:1 to pembrolizumab 200 mg (n=410) or placebo (n=206) every 3 weeks (for up to 35 cycles, approximately 2 years) plus 4 cycles of pemetrexed (500 mg/m<sup>2</sup>) and investigators' choice of cisplatin (75 mg/m<sup>2</sup>) or carboplatin (AUC 5 mg/ml/min) every 3 weeks, followed by pemetrexed until progression. Patients assigned to placebo plus pemetrexed-platinum could crossover to pembrolizumab upon progression if eligibility criteria were met. The primary endpoints were OS and PFS. **RESULTS:** After median follow-up of 31.0 months, pembrolizumab plus pemetrexed-platinum continued to improve OS (hazard ratio [HR], 0.56; 95% CI, 0.46–0.69), and PFS (HR, 0.49; 95% CI, 0.41–0.59) over placebo plus pemetrexed-platinum regardless of PD-L1 expression. ORR (48.3% versus 19.9%) and time to second/subsequent tumor progression on next-line treatment (PFS2; HR, 0.50; 95% CI, 0.41–0.61) were improved in patients who received pembrolizumab plus pemetrexed-platinum. 84 patients (40.8%) from the placebo plus pemetrexed-platinum group crossed over to pembrolizumab on-study. Grade 3–5 adverse events occurred in 72.1% of patients receiving pembrolizumab plus pemetrexed-platinum and 66.8% of patients receiving placebo plus pemetrexed-platinum. 56 patients completed 35 cycles (approximately 2 years) of pembrolizumab; ORR was 85.7% and 53 (94.6%) were alive at data cutoff. **CONCLUSION:** Pembrolizumab plus pemetrexed-platinum continued to show improved efficacy outcomes compared with placebo plus pemetrexed-platinum, with manageable toxicity. These findings support first-line pembrolizumab plus pemetrexed-platinum in patients with previously untreated metastatic nonsquamous NSCLC.

### [Evaluation of Pathologic Response in Lymph Nodes of Patients With Lung Cancer Receiving Neoadjuvant Chemotherapy](#)

J Thorac Oncol. 2021 Apr 20;S1556-0864(21)02109-2. doi: 10.1016/j.jtho.2021.03.029. Online ahead of print. Apar Pataer 1 , Annikka Weissferdt 2 , Ara A Vaporciyan 3 , et al.

**INTRODUCTION:** Major pathologic response (MPR), defined as residual viable tumor of less than or equal to 10%, currently serves as a surrogate end point for survival for patients with resectable NSCLC after neoadjuvant chemotherapy. However, the significance of pathologic response in lymph nodes harboring metastatic tumors in such patients remains uncertain. Therefore, we studied the effect of neoadjuvant chemotherapy on resected positive lymph nodes and determined if the degree of pathologic response in the lymph nodes alone (LN-MPR) or in combination with that of the primary tumor (PT-MPR) was able to predict the outcome. **METHODS:** A total of 75 patients with NSCLC who underwent neoadjuvant chemotherapy and completed surgical resection were included in this study. Tissue specimens were retrospectively evaluated by two pathologists blinded to the patients' treatments and outcomes. Specimens were reviewed for the degree of pathologic response in the primary tumor and in any involved lymph nodes. The prognostic performance of LN-MPR alone or in combination with PT-MPR with respect to overall survival (OS) was evaluated using the Kaplan-Meier method and Cox regression model. **RESULTS:** LN-MPR was significantly predictive of long-term OS after neoadjuvant

chemotherapy. A combination of PT-MPR with LN-MPR was significantly associated with outcome and allowed stratification of patients into three prognostic groups ( $p = 0.001$ ). **CONCLUSIONS:** LN-MPR in isolation is a reliable predictor of OS in patients with NSCLC receiving neoadjuvant chemotherapy. A combination of LN-MPR with PT-MPR seems to correlate well with the outcome and can be used to predict prognosis in this patient population.

**Pembrolizumab Plus Chemotherapy or Anlotinib vs. Pembrolizumab Alone in Patients With Previously Treated EGFR-Mutant NSCLC** Front Oncol. 2021 Apr 16;11:671228. doi:

10.3389/fonc.2021.671228. eCollection 2021. Ya Chen 1, Zhengyu Yang 1, et al.

**OBJECTIVES:** More and more encouraging evidence revealed that immunotherapy could improve clinical outcomes in patients with previously treated non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) variations. However, immunotherapy is still a controversy for NSCLC patients with EGFR mutation. **METHOD:** In this retrospective analysis, we compared the clinical efficacy of pembrolizumab monotherapy (PM), pembrolizumab combined with chemotherapy (P+C) and pembrolizumab combined with anlotinib (P+A) in NSCLC patients with EGFR mutation who had failed on EGFR-TKI and platinum-based chemotherapy. **RESULT:** Eighty-six patients were included in this study. The overall median progression free survival (PFS) was 3.24 months. Multivariate analysis suggested that EGFR L858R and combined therapy were positive prognostic factors of PFS. The overall median OS was 12.28 months. Multivariate analysis found that high PD-L1 expression ( $\geq 50\%$ ) and combined therapy seemed to be positive prognostic factors of OS. Among the population, 32 patients received PM, 26 patients received P+C and 28 patients received P+A. Up to Jan 30, 2021, the median progression-free survival was 1.5 months in the PM group, 4.30 months in the P+C group and 3.24 months in the P+A group. The median OS were 7.41, 14.92 and 15.97 months, respectively. The ORR were 3.1%, 23.1% and 21.4%. **CONCLUSION:** The addition of chemotherapy or antiangiogenic therapy to pembrolizumab resulted in significantly longer PFS, OS and ORR than pembrolizumab alone in our study. EGFR L858R might be a positive prognostic factor of PFS and high PD-L1 expression might be a positive prognostic factor of OS.

**Perilesional edema in brain metastases as predictive factor of response to systemic therapy in non-small cell lung cancer patients: a preliminary study** Ann Transl Med. 2021 Apr;9(8):648. doi:

10.21037/atm-20-6497. Montse Alemany 1, Marta Domènech 2, Andreas A Argyriou 3, et al.

Noelia Vilariño 1 2, Carles Majós 1 4, Pablo Naval-Baudin 4, Anna Lucas 1, Ramón Palmero 2,

**BACKGROUND:** The significance of upfront systemic therapies as an alternative to whole brain radiotherapy (WBRT) for multiple brain metastases (BM) is debatable. Our purpose is to investigate if peritumoral edema could predict the intracranial response to systemic chemotherapy (chemo) in patients with advanced non-squamous non-small cell lung cancer (non-SQ-NSCLC) and synchronous multiple BM. **METHODS:** In this observational cohort study, we evaluated the outcome of 28 patients with multiple BM ( $\geq 3$ ) treated with chemo based on cisplatin/carboplatin plus pemetrexed (chemo, group A,  $n=17$ ) or WBRT plus subsequent chemo (group B,  $n=11$ ). The intracranial response, assessed by the response assessment neuro-oncology (RANO) BM criteria, was correlated with the degree of BM-associated edema estimated by the maximum diameter ratio among fluid attenuated inversion recovery (FLAIR) and gadolinium-enhanced T1WI (T1Gd) per each BM at the baseline brain magnetic resonance imaging (MRI). **RESULTS:** No differences were observed in baseline characteristics between both groups, except for the number of patients under steroid treatment that was clearly superior in group B ( $P=0.007$ ). Median OS was similar between groups. Regarding FLAIR/T1Gd ratio (F/Gd), patients treated with chemo alone exhibited significantly higher values ( $P=0.001$ ) in those who developed intracranial progression disease (PD) ( $2.80 \pm 0.32$  mm), compared with those who achieved partial response (PR) ( $1.30 \pm 0.11$  mm) or stable disease (SD) ( $1.35 \pm 0.09$  mm). In patients treated with WBRT, F/Gd ratio was

not predictive of response. **CONCLUSIONS:** Peritumoral edema estimated by F/Gd ratio appears a promising predictive tool to identify oligosymptomatic patients with multiple BM in whom WBRT can be postponed.

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## NSCLC - RADIOTHERAPY

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### [Local failure after stereotactic radiosurgery \(SRS\) for intracranial metastasis: analysis from a cooperative, prospective national registry](#)

J Neurooncol. 2021 Apr;152(2):299-311. doi: 10.1007/s11060-021-03698-7. Epub 2021 Jan 22. Anthony L Asher 1 , Mohammed Ali Alvi 2 , et al.

**INTRODUCTION:** Stereotactic radiosurgery (SRS) has been increasingly employed to treat patients with intracranial metastasis, both as a salvage treatment after failed whole brain radiation therapy (WBRT) and as an initial treatment. "Several studies have shown that SRS may be as effective as WBRT with the added benefit of preserving neuro-cognition". However, some patients may have local failure following SRS for intracranial metastasis, defined as increase in total lesion volume by 25% after at least 3 months of follow up. **METHODS:** The SRS registry, established by the Neuro point alliance (NPA) under the auspices of the American Association of Neurological Surgeons (AANS), was queried for patients with intracranial metastasis receiving SRS at the participating sites. Demographic, clinical symptoms, tumor, and treatment characteristics as well as follow up status were summarized for the cohort. A multivariable explanatory cox- regression was performed to evaluate the impact of each of the factors on time to local failure.at last follow-up. **RESULTS:** A total of 441 patients with 1255 intracranial metastatic lesions undergoing SRS were identified. The most common primary cancer histology was non-small cell lung cancer (43.8%, n = 193). More than half of the cohort had more than 1 metastatic lesion (2-3 lesions: 29.5%, n = 130; more than 3 lesions: 25.2% (n = 111). The average duration of follow-up for the cohort was found to be 8.4 months (SD = 7.61). The mean clinical treatment volume (CTV), after adding together the volume of each lesion for each patient was 5.39 cc (SD = 7.6) at baseline. A total of 20.2% (n = 89) had local failure (increase in volume by > 25%) with a mean time to progression of 7.719 months (SD = 6.09). The progression free survival (PFS) for the cohort at 3, 6 and 12 months were found to be 94.9%, 84.3%, and 69.4%, respectively. On multivariable cox regression analysis, factors associated with increased hazard of local failure included male gender (HR 1.65, 95% CI 1.03-2.66, p = 0.037), chemotherapy at or before SRS (HR = 2.39, 95% CI 1.41-4.05, p = 0.001), WBRT at or before SRS (HR = 2.21, 95% CI 1.16- 4.22, p = 0.017), while surgical resection (HR 0.45, 95% CI 0.21-0. 97, p = 0.04) and immunotherapy (0.34, 95% CI 0.16-0.50, p = 0.014) were associated with lower hazard of local failure. **CONCLUSION:** Factors found to be predictive of local failure included higher RPA score and those receiving chemotherapy, while patients undergoing surgical resection and those with occipital lobe lesions were less likely to experience local failure. Our analyses not only corroborate those previously reported but also demonstrate the utility of a multi-institutional registry to advance real-world SRS research for patients with intracranial metastatic lesions.

### [Systemic effect of radiotherapy before or after nivolumab in lung cancer: an observational, retrospective, multicenter study](#)

Tumori. 2021 Apr 4;3008916211004733. doi:

10.1177/03008916211004733. Online ahead of print. Maria Bassanelli 1 , Biagio Ricciuti 2 , Diana Giannarelli 3 , et al.

**BACKGROUND:** The combination of radiotherapy (RT) and programmed death 1 inhibitors seems to increase antitumor immune responses. **OBJECTIVE:** To assess the outcome and the role of the best combination sequence, i.e. immunotherapy given before, during, and/or after RT, in patients with non-small cell lung cancer (NSCLC). **METHODS:** We conducted an observational, retrospective analysis of 95 consecutive patients with advanced NSCLC who received any radiotherapy treatment and nivolumab,

as clinically indicated. Median overall survival (OS) and the 95% confidence interval (CI) were estimated with the Kaplan-Meier method. Cox model was used to obtain hazard ratio (HR) and associated 95% CI with statistical inference by log-rank statistic. **RESULTS:** Median OS was 11.9 months (95% CI, 6.6-17.2). Patients who received radiotherapy during an immune checkpoint inhibitor treatment started more than 60 days before showed a better outcome than patients who started immunotherapy over 60 days after RT ending (HR, 2.90 [1.37-6.12],  $p = 0.005$ ; median OS, 22.4 months vs 8.6 months,  $p = 0.005$ ). Median progression-free survival was 6.3 months (95% CI, 4.6-8.0). **CONCLUSIONS:** This study shows that combining irradiation with nivolumab for the treatment of advanced NSCLC leads to improved OS. The optimal time window for the combination of RT and immunotherapy seems to play a critical role for therapeutic antitumor response derived by abscopal effect.

**[Radiomics predicts risk of cachexia in advanced NSCLC patients treated with immune checkpoint inhibitors](#)** Br J Cancer. 2021 Apr 7. doi: 10.1038/s41416-021-01375-0. Online ahead of print. Wei Mu <sup>1</sup>, Evangelia Katsoulakis <sup>2</sup>, Christopher J Whelan <sup>1</sup>, Kenneth L Gage <sup>3</sup>, Matthew B Schabath <sup>4 5</sup>, Robert J Gillies <sup>6</sup>

**BACKGROUND:** Approximately 50% of cancer patients eventually develop a syndrome of prolonged weight loss (cachexia), which may contribute to primary resistance to immune checkpoint inhibitors (ICI). This study utilised radiomics analysis of 18F-FDG-PET/CT images to predict risk of cachexia that can be subsequently associated with clinical outcomes among advanced non-small cell lung cancer (NSCLC) patients treated with ICI. **METHODS:** Baseline (pre-therapy) PET/CT images and clinical data were retrospectively curated from 210 ICI-treated NSCLC patients from two institutions. A radiomics signature was developed to predict the cachexia with PET/CT images, which was further used to predict durable clinical benefit (DCB), progression-free survival (PFS) and overall survival (OS) following ICI.

**RESULTS:** The radiomics signature predicted risk of cachexia with areas under receiver operating characteristics curves (AUCs)  $\geq 0.74$  in the training, test, and external test cohorts. Further, the radiomics signature could identify patients with DCB from ICI with AUCs  $\geq 0.66$  in these three cohorts. PFS and OS were significantly shorter among patients with higher radiomics-based cachexia probability in all three cohorts, especially among those potentially immunotherapy sensitive patients with PD-L1-positive status ( $p < 0.05$ ). **CONCLUSIONS:** PET/CT radiomics analysis has the potential to predict the probability of developing cachexia before the start of ICI, triggering aggressive monitoring to improve potential to achieve more clinical benefit.

**[Higher biologically effective dose is associated with improved survival in patients with squamous cell carcinoma of the lung treated with stereotactic body radiation therapy](#)** Radiother Oncol. 2021 Apr 21;160:25-31. doi: 10.1016/j.radonc.2021.04.010. Online ahead of print. Jacob S Parzen <sup>1</sup>, Muayad F Almahariq <sup>2</sup>, Thomas J Quinn <sup>1</sup>, Zaid A Siddiqui <sup>3</sup>, Andrew B Thompson <sup>1</sup>, Thomas Guerrero <sup>1</sup>, Kuei Lee <sup>1</sup>, Craig Stevens <sup>1</sup>, Inga S Grills <sup>1</sup>

**BACKGROUND:** Multiple studies have suggested that patients with early-stage SCC of the lung treated with SBRT are more susceptible to local failure compared to other NSCLC histologies. It is unknown if higher BED leads to improved outcomes in this patient population. We evaluated the effect of "high" BED versus "low" BED SBRT on overall survival (OS) in SCC and non-SCC NSCLC patients.

**METHODS:** The National Cancer Database was used to identify patients with cT1-2N0M0 NSCLC diagnosed between 2006-2016 treated with 3-5 fraction SBRT. Patients were grouped by BED<sub>high</sub> ( $>150$  Gy) and BED<sub>low</sub> ( $\leq 132$  Gy). Univariate and multivariable analysis using Kaplan-Meier and Cox proportional hazards regression modeling were performed. Propensity-score matched analysis with inverse probability of treatment (IPTW) weighting was used to account for selection bias. **RESULTS:** We identified 4,717 eligible SCC patients and 8,807 eligible non-SCC NSCLC patients. In SCC patients, BED<sub>high</sub> was associated with improved OS in both univariate and multivariate analysis (MVA HR 0.84



95% CI 0.76-0.92,  $p < 0.001$ ), with estimated IPTW-adjusted 3-year OS of 49% compared to 41% for the BEDlow group. In contrast, BEDhigh was not associated with improved OS compared to BEDlow for non-SCC NSCLC patients (MVA HR 0.94 95% CI 0.86-1.04,  $p = 0.23$ ), with estimated IPTW-adjusted 3-year OS of 54% and 53%, respectively. **CONCLUSIONS:** Our analysis suggests that in patients with early-stage NSCLC, SBRT regimens with BED > 150 Gy may confer a survival benefit in patients with SCC histology. Histology-based dose modification should be considered, and prospective validation may be warranted.

**[The HILUS-Trial-a Prospective Nordic Multicenter Phase 2 Study of Ultracentral Lung Tumors Treated With Stereotactic Body Radiotherapy](#)** J Thorac Oncol. 2021 Apr 3;S1556-0864(21)02074-8. doi: 10.1016/j.jtho.2021.03.019. Online ahead of print. Karin Lindberg 1, Vitali Grozman 2, Kristin Karlsson 3, et al.

**INTRODUCTION:** Stereotactic body radiation therapy of thoracic tumors close to the central airways implies risk of severe toxicity. We report a prospective multicenter phase 2 trial for tumors located less than or equal to 1 cm from the proximal bronchial tree with primary end point of local control and secondary end point of toxicity. **METHODS:** Stereotactic body radiation therapy with 7 Gy  $\times$  8 was prescribed to the 67% isodose encompassing the planning target volume. The patients were stratified to group A (tumors  $\leq$  1 cm from the main bronchi and trachea) or group B (all other tumors). Risk factors for treatment-related death were tested in univariate analysis, and a logistic regression model was developed for fatal bronchopulmonary bleeding versus dose to the main bronchi and trachea.

**RESULTS:** A total of 65 patients (group A/group B,  $n = 39/26$ ) were evaluated. The median distance between the tumor and the proximal bronchial tree was 0 mm (0-10 mm). The 2-year local control was 83%. Grade 3 to 5 toxicity was noted in 22 patients, including 10 cases of treatment-related death (bronchopulmonary hemorrhage,  $n = 8$ ; pneumonitis,  $n = 1$ ; fistula,  $n = 1$ ). Dose to the combined structure main bronchi and trachea and tumor distance to the main bronchi were important risk factors. Dose modeling revealed minimum dose to the "hottest" 0.2 cc to the structure main bronchi and trachea as the strongest predictor for lethal bronchopulmonary hemorrhage. **CONCLUSIONS:** On the basis of the presented data, 7 Gy  $\times$  8, prescribed to the planning target volume-encompassing isodose, should not be used for tumors located within 1 cm from the main bronchi and trachea. Group B-type tumors may be considered for the treatment on the basis of an individual risk-benefit assessment and a maximum dose to the main bronchi and trachea in the order of 70 to 80 Gy (equivalent dose in 2 Gy fractions).

**[Stereotactic body radiotherapy with a high maximum dose improves local control, cancer-specific death and overall survival in peripheral early-stage non-small cell lung cancer](#)** Int J Radiat Oncol Biol Phys. 2021 Apr 20;S0360-3016(21)00375-8. doi: 10.1016/j.ijrobp.2021.04.014. Online ahead of print. Yudai Tateishi 1, Atsuya Takeda 2, Nobuyuki Horita 3, Yuichiro Tsurugai 4, Takahisa Eriguchi 5, Yuichi Kibe 6, Naoko Sanuki 7, Takeshi Kaneko 8

**PURPOSE:** We investigated whether delivery of a high biologically effective dose (BED) to primary tumors affects systemic outcomes of cancer-specific death (CSD) and overall survival (OS) rates following stereotactic body radiotherapy (SBRT) in patients with early-stage non-small cell lung cancer (ES-NSCLC). **PATIENTS AND METHODS:** Among consecutive ES-NSCLC patients treated with SBRT between 2005 and 2019, we retrospectively identified patients who received a prescription of 50-60 Gy/5 fractions with maximum doses of 62.5-100 Gy. Patients were categorized by maximum BED within the planning target volume with a threshold dose of 200 Gy. Outcomes were analyzed in all and matched patients. **RESULTS:** Overall, 433 patients were eligible, and 262 and 171 patients were categorized into HighBED- and LowBED-groups, respectively. After propensity score matching, pairs of 154 patients were selected. Median follow-up times for the HighBED- and LowBED-groups were 52.3 months (range, 0.8-107.2 months) and 121.6 months (range, 3.0-162.8 months), respectively. The local recurrence rate in

the HighBED-group was significantly lower than that in the LowBED-group (5 years rate, 1.3% and 7.2%; hazard ratio (HR), 0.15; 95% CI, 0.03 to 0.65; p=.011). Rates of any recurrence and CSD in the HighBED-group were significantly lower (any recurrence: 5 years rate; 18.1% and 32.1%; HR, 0.52; 95% CI, 0.33 to 0.83; p=.0058; CSD: 5 years rate, 9.5% and 21.8%; HR, 0.38; 95% CI, 0.20 to 0.70; p=.002) and OS in the HighBED-group was significantly better compared with the LowBED-group (5 years rate, 61.7% and 51.8%; HR, 0.71; 95% CI, 0.50 to 1.00; p=.047). **CONCLUSION:** In patients with peripheral ES-NSCLC, SBRT with a high maximum dose may improve not only local control, but also any recurrence, CSD, and OS rates without increased toxicity. Further trials designed to evaluate whether higher-intensity SBRT increases local control rates and contributes to improved CSD and OS outcomes are anticipated.

**[Radiation and Modulation of the Tumor Immune Microenvironment in Non-Small Cell Lung Cancer](#)** Semin Radiat Oncol. 2021 Apr;31(2):133-139. doi: 10.1016/j.semradonc.2020.11.010.

Peter H Goff<sup>1</sup>, Jing Zeng<sup>2</sup>, Ramesh Rengan<sup>2</sup>, Stephanie K Schaub<sup>2</sup>

Immune checkpoint inhibitors are approved for a variety of indications for locally advanced and metastatic non-small cell lung cancer (NSCLC), and trials are ongoing in the early-stage setting. There is an unmet need to understand which patients may derive benefit from immunotherapies and how to harness combined modality therapies to improve overall response rates and durability. Here, we review studies from the bench-to-bedside to examine the role of radiation therapy (RT) on the tumor immune microenvironment in NSCLC with an eye toward augmenting antitumor immunity. Together, these data provide a foundation for developing future clinical trials harnessing RT to augment antitumor immunity and highlight the need for correlative translational studies to directly characterize the impact of RT on the human NSCLC tumor immune microenvironment.

**[Impact of Radiotherapy Pattern on the Prognosis of Stage IV Lung Adenocarcinomas Harboring EGFR Mutations](#)** Cancer Manag Res. 2021 Apr 15;13:3293-3301. doi: 10.2147/CMAR.S299563.

eCollection 2021. Yingyun Zhang<sup>1 2</sup>, Wei Wang<sup>1 2</sup>, Xuedong Xu<sup>1 2</sup>, Yankang Li<sup>1 3</sup>, Hui Zhang<sup>4</sup>, Jianbin Li<sup>1 2</sup>, Zhenxiang Li<sup>1</sup>

**INTRODUCTION:** The aim of this study was to investigate the role of local radiotherapy in the management of epidermal growth factor receptor (EGFR)-mutant non-small cell lung cancers (NSCLCs) treated with EGFR tyrosine kinase inhibitors (TKIs). **MATERIALS AND METHODS:** Patients with stage IV EGFR-mutant NSCLC treated with radiotherapy concomitant to EGFR TKIs from May 2010 to December 2017 were retrospectively identified. Overall survival (OS) was the primary endpoints of the study. **RESULTS:** A total of 205 patients were enrolled in the study. One hundred eleven patients received one-time single-site radiotherapy (SSR), and 94 patients received multiple-site radiotherapy (MSR). Patients who received MSR had longer OS (median OS, 40.0 months; 95% confidence interval [CI], 29.6 to 50.4) than those who received SSR (median OS, 28.9 months; 95% CI, 24.3 to 33.5; P=0.031). Thoracic radiotherapy was associated with prolonged median OS (41.7 months, 95% CI, 29.0 to 54.4 vs 27.1 months, 95% CI 22.7 to 31.5; log-rank P<0.001). Multivariate analysis confirmed that thoracic radiotherapy was independently associated with improved OS (adjusted hazard ratio [HR], 0.514; 95% CI 32.3% to 81.8%; P=0.005). **CONCLUSION:** MSR improves survival outcomes in patients with advanced-stage, EGFR-mutant, lung adenocarcinoma, with thoracic radiotherapy having the most significant effect on prognosis.

[Efficacy and Safety of Niraparib as Maintenance Treatment in Patients with Extensive-Stage Small Cell Lung Cancer after First-Line Chemotherapy: A Randomized, Double-Blind, Phase 3 Study](#)

J Thorac Oncol. 2021 Apr 26;S1556-0864(21)02111-0. doi: 10.1016/j.jtho.2021.04.001. Online ahead of print. Xinghao Ai <sup>1</sup>, Yueyin Pan <sup>2</sup>, Jianhua Shi <sup>3</sup>, et al.

**INTRODUCTION:** ZL-2306-005 is a randomized, double-blind, multicenter phase 3 study evaluating the efficacy and safety of niraparib, a poly(ADP-ribose) polymerase inhibitor, as first-line maintenance therapy in Chinese patients with platinum-responsive, extensive-stage small cell lung cancer (ES-SCLC). **METHODS:** Patients with complete/partial response (CR/PR) to standardized, platinum-based first-line chemotherapy were randomized 2:1 to receive niraparib or placebo (300 mg [baseline body weight  $\geq$ 77 kg, platelet count  $\geq$ 150,000/ $\mu$ L] or 200 mg) once daily until progression or unacceptable toxicity. Primary endpoints were progression-free survival (PFS) (blinded independent central review, BICR) and overall survival (OS) (sample size planned: 591 patients). Secondary endpoints included investigator-assessed PFS and safety. **RESULTS:** ZL-2306-005 was terminated early due to ES-SCLC treatment landscape changes (data cut-off: 20 Mar 2020). During July 2018-February 2020, 185 of 272 patients screened were randomized (niraparib: n=125 [CR=1, PR=124]; placebo: n=60 [CR=1, PR=59]). Median (95% confidence interval [CI]) PFS (BICR) was 1.54 months (1.41-2.69, niraparib) and 1.36 months (1.31-1.48, placebo); hazard ratio [HR]=0.66 (95% CI: 0.46-0.95; p=0.0242). Median OS was 9.92 months (9.33-13.54, niraparib) and 11.43 months (9.53-not estimable, placebo); HR=1.03 (95% CI: 0.62-1.73; p=0.9052). Median investigator-assessed PFS was 1.48 months (1.41-2.56, niraparib) and 1.41 months (1.31-2.00, placebo); HR=0.88 (95% CI: 0.61-1.26; p=0.4653). Grade  $\geq$ 3 adverse events occurred in 34.4% (niraparib) and 25.0% (placebo) of patients. **CONCLUSIONS:** ZL-2306-005 did not reach primary endpoints. However, niraparib as maintenance therapy modestly improved PFS in patients with platinum-responsive ES-SCLC, with acceptable tolerability profile and no new safety signal.

[Chemotherapy in idiopathic pulmonary fibrosis and small-cell lung cancer with poor lung function](#)

BMC Pulm Med. 2021 Apr 15;21(1):122. doi: 10.1186/s12890-021-01489-4. Xiyue Zhang <sup>1</sup>, Wei Li <sup>1</sup>, Chunyan Li <sup>1</sup>, Jie Zhang <sup>2</sup>, Zhenzhong Su <sup>3</sup>

**BACKGROUND:** Idiopathic pulmonary fibrosis (IPF) is a chronic interstitial lung disease with unclear pathogenesis. IPF is considered as a risk factor for lung cancer. Compared to other lung cancers, small-cell lung cancer (SCLC) has a lower incidence, but has a more aggressive course. Patients with IPF and SCLC have a lower survival rate, more difficult treatment, and poorer prognosis. **CASE**

**PRESENTATION:** Case 1 was of a 66-year-old man with IPF for 5 years, who was admitted to our hospital for dyspnea. Case 2 was of a 68-year-old woman, who presented with chest pains, cough, and dyspnea. Both patients had extremely poor lung function. High-resolution computed tomography and pathology revealed that both patients had IPF and SCLC. Chemotherapy comprising nedaplatin (80 mg/m<sup>2</sup>) and etoposide (100 mg for 5 days) was initiated for both patients. Antifibrotic agents were continued during the chemotherapeutic regimen. Both patients showed improvement in their condition after treatment. **CONCLUSION:** The favorable outcomes in these 2 cases suggests that chemotherapy is worth considering in the management of patients having SCLC and IPF with poor lung function.

[Promising Role of Circulating Tumor Cells in the Management of SCLC](#)

Cancers (Basel). 2021 Apr 22;13(9):2029. doi: 10.3390/cancers13092029. Antonella De Luca <sup>1</sup>, Marianna Gallo <sup>1</sup>, Claudia Esposito <sup>1</sup>, Alessandro Morabito <sup>2</sup>, Nicola Normanno <sup>1</sup>

Small cell lung cancer is an aggressive disease for which few therapeutic options are currently available. Although patients initially respond to therapy, they rapidly relapse. Up to today, no biomarkers for guiding treatment of SCLC patients have been identified. SCLC patients rarely undergo surgery and often

the available tissue samples are inadequate for biomarker analysis. Circulating tumor cells (CTCs) are rare cells in the peripheral blood that might be used as surrogates of tissue samples. Different methodological approaches have been developed for studies of CTCs in SCLC. In addition to CTC count, which might provide prognostic and predictive information, genomic and transcriptomic analyses allow the characterization of molecular profiles of CTCs and permit the study of tumor heterogeneity. The employment of CTC-derived xenografts offers complementary information to genomic analyses and CTC enumeration about the mechanisms involved in the sensitivity/resistance to treatments. Using these approaches, CTC analysis is providing relevant information on SCLC biology that might aid in the development of personalized therapeutic strategies for SCLC patients.

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## PALLIATIVE AND SUPPORTIVE CARE

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### [Symptom Treatment Preferences of Cancer Survivors: Does Fatigue Level Make a Difference?](#)

Cancer Nurs. 2021 Apr 21. doi: 10.1097/NCC.0000000000000941. Online ahead of print. Ellen Krueger 1 , Ekin Secinti, Catherine E Mosher, Patrick V Stutz, Andrea A Cohee, Shelley A Johns

**BACKGROUND:** Cancer-related fatigue (CRF) is among the most prevalent symptoms in cancer survivors and often co-occurs with other symptoms. However, little is known about survivors' preferences for treating CRF and associated symptoms. **OBJECTIVE:** The aim of this study was to examine cancer survivors' interest in learning skills to manage CRF and associated symptoms and their interest in various nonpharmacologic interventions and modalities. These outcomes were compared between survivors with high and normal fatigue. **METHODS:** Breast, gastrointestinal, lung, and prostate cancer survivors (N = 338) completed a 1-time survey, including a Patient-Reported Outcomes Measurement Information System fatigue measure and a checklist assessing interest in learning skills to manage CRF and associated symptoms as well as interest in nonpharmacologic interventions and modalities. **RESULTS:** Many cancer survivors reported interest in learning skills to manage CRF (range, 35%-78%) and associated symptoms (range, 13%-48%). Compared with survivors with normal fatigue (n = 180), highly fatigued survivors (n = 158; Patient-Reported Outcomes Measurement Information System fatigue T score  $\geq$  55) were more likely to report interest in learning skills to manage various symptoms, self-compassion training, and programs offered individually and in person. Interest in other interventions and modalities did not vary by fatigue level. **CONCLUSIONS:** Many cancer survivors, especially those with high fatigue, report interest in learning symptom management skills. Given survivors' high level of interest in complementary and integrative health interventions, future research should continue to assess their impact on symptoms and functioning. **IMPLICATIONS FOR PRACTICE:** Nurses can offer a menu of evidence-based options for symptom management, given survivors' diverse preferences. Nurses can also provide psychoeducation regarding their preferred treatments.

### ["Randomized trial of physical activity on quality of life and lung cancer biomarkers in patients with advanced stage lung cancer: a pilot study"](#)

BMC Cancer. 2021 Apr 1;21(1):352. doi: 10.1186/s12885-021-08084-0. Brett C Bade 1 , Geliang Gan 2 , Fangyong Li 2 , Lingeng Lu 3 , Lynn Tanoue 4 , Gerard A Silvestri 5 , Melinda L Irwin 3

**BACKGROUND:** Lung cancer survivors need more options to improve quality of life (QoL). It is unclear to what extent patients with advanced stage disease are willing to participate in home-based physical activity (PA) and if these interventions improve QoL. The goal of our study was to determine interest in participating in our 3-month home-based walking regimen in patients with advanced stage lung cancer. We used a randomized design to evaluate for potential benefit in PA and patient-reported outcomes. **METHODS:** We performed an open-label, 1:1 randomized trial in 40 patients with stage III/IV non-small cell lung cancer (NSCLC) evaluating enrollment rate, PA, QoL, dyspnea, depression, and biomarkers. Compared to usual care (UC), the intervention group (IG) received an accelerometer, in-

person teaching session, and gain-framed text messages for 12 weeks. **RESULTS:** We enrolled 56% (40/71) of eligible patients. Participants were on average 65 years and enrolled 1.9 years from diagnosis. Most patients were women (75%), and receiving treatment (85%) for stage IV (73%) adenocarcinoma (83%). A minority of patients were employed part-time or full time (38%). Both groups reported low baseline PA (IG mean 37 (Standard deviation (SD) 46) vs UC 59 (SD 56) minutes/week;  $p = 0.25$ ). The IG increased PA more than UC (mean change IG + 123 (SD 212) vs UC + 35 (SD 103) minutes/week;  $p = 0.051$ ). Step count in the IG was not statistically different between baseline (4707 step/day), week 6 (5605;  $p = 0.16$ ), and week 12 (4606 steps/day;  $p = 0.87$ ). The intervention improved EORTC role functioning domain (17 points;  $p = 0.022$ ) with borderline improvement in dyspnea (- 13 points;  $p = 0.051$ ) compared to UC. In patients with two blood samples (25%), we observed a significant increase in soluble PD-1 (219.8 (SD 54.5) pg/mL;  $p < 0.001$ ). **CONCLUSIONS:** Our pilot trial using a 3-month, home-based, mobile health intervention enrolled over half of eligible patients with stage III and IV NSCLC. The intervention increased PA, and may improve several aspects of QoL. We also identified potential biomarker changes relevant to lung cancer biology. Future research should use a larger sample to examine the effect of exercise on cancer biomarkers, which may mediate the association between PA and QoL

[Distress experienced by lung cancer patients and their family caregivers in the first year of their cancer journey](#) Palliat Support Care. 2021 Apr 26;1-7. doi: 10.1017/S1478951521000377. Online ahead of print. Michèle Aubin 1 2 3 , Lucie Vézina 1 , René Verreault 3 , et al.

**OBJECTIVES:** Diagnosis of cancer is emotionally threatening not only for patients but also for their family caregivers (FC) who witness and share much of the illness experience. This study compares distress experienced by lung cancer patients and their FC during the year following the diagnosis. **METHODS:** A prospective cohort study of 206 patients recently diagnosed with inoperable lung cancer (participation rate 79.5%) and 131 FC (participation rate 63.6%) was conducted in an ambulatory oncology clinic in Quebec City (Canada). They completed validated questionnaires regarding their personal and psychological characteristics (Hospital and Anxiety Depression Scale-HADS), in the first months after the diagnosis of lung cancer and after 6 and 12 months. Univariate, bivariate, and linear mixed models were conducted to compare patient and FC distress. **RESULTS:** At baseline, 7.8% of patients reported distress (HADS total score  $>15$ ) and their mean distress score was  $7.0 \pm 4.9$  (range 0-42). In contrast, 33.6% of FC presented significant distress and their mean distress score was  $12.0 \pm 7.2$  ( $P < 0.0001$ ). Proportions of patients and FC with distress remained relatively stable at 6 and 12 months, and at every time point, FC reported higher levels of distress compared to their relative with cancer ( $P < 0.0001$ ). Comparable trends were found when looking at the mean scores of distress, anxiety, and depression throughout the study. **SIGNIFICANCE OF RESULTS:** Being diagnosed with lung cancer and going through its different phases seems to affect more FC than patients. The psychological impact of such diagnosis appears early after the diagnosis and does not significantly change over time. These findings reinforce the importance for oncology teams, to include FC in their systematic distress screening program, in order to help them cope with their own feelings and be able to play their role in patient support and care throughout the cancer journey.

[Functional Decline as an Indicator of Ill-Health: A Retrospective Case Study of the Process Leading to Lung Cancer](#) J Multidiscip Healthc. 2021 Apr 27;14:919-927. doi: 10.2147/JMDH.S295498.

eCollection 2021. Lesleigh Kowalski 1

**PURPOSE:** Lung cancer claims more lives than any cancer in the world and remains difficult to diagnosis at early stages. Detecting lung cancer is challenging due to nonspecific symptom presentation. Literature was reviewed to consider functional decline as an indicator for ill-health. This study explored the process experienced from recognition in a change of health to receiving a lung cancer diagnosis from

a patient's perspective in order to examine this phase through a biopsychosocial lens. **PATIENTS AND METHODS:** A single-case design methodology was used for this study. The method of data collection was semi-structured interviews with people diagnosed with lung cancer utilizing criterion sampling. The case study was bound by diagnostic and geographical factors to frame the single-case: participants were limited to those living in Alaska diagnosed with stage III or stage IV lung cancer. **RESULTS:** One (n = 1) person participated in this study. Themes consistent with lung cancer detection process from a patient's perspective include symptom denial, symptom reductionism, and gradual impact on function. **CONCLUSION:** Although the number of participants was extremely limited due to the COVID-19 pandemic at the time of recruitment, this case study suggests a decline in function present prior to being diagnosed with lung cancer. Opportunities exist within the provider and patient interface to promote earlier detection include educating medical providers to ask specific, closed-ended, non-disease related functional questions to ascertain more details and a holistic representation of patients' health. Raising public awareness of lung cancer symptoms, such as fatigue and dyspnea, is also warranted.

**[Incidence and Risk Factors of Pneumonitis in Patients with Non-Small Cell Lung Cancer: An Observational Analysis of Real-World Data](#)** Oncol Ther. 2021 Apr 28. doi: 10.1007/s40487-021-00150-8. Online ahead of print. Jerzy E Tyczynski 1 , Ravi Potluri 2 , Ryan Kilpatrick 3 , Debasish Mazumder 4 , Anirban Ghosh 4 , Alexander Liede 3 5

**INTRODUCTION:** The incidence of pneumonitis, a treatment-related adverse event (AE) in non-small cell lung cancer (NSCLC) patients, has been studied in the United States mostly through clinical trials and retrospective chart reviews. Few analyses of real-world data have been published. This study of a large nationally representative health records database estimated the incidence and predictors of pneumonitis among treated NSCLC patients between 2008 and 2018. **METHODS:** The Optum® electronic health records (EHR) database includes data on over 80 million patients from more than 50 healthcare plans. The cohort of primary NSCLC patients was identified using ICD-9/10 codes. Natural language processing of unstructured data from physicians' notes facilitated extraction of biomarker (epidermal growth factor receptor [EGFR] and programmed death ligand-1 [PD-L1]) status. Cumulative incidence was estimated as the proportion with pneumonitis overall, by clinical characteristics, and line of therapy (LOT) after diagnosis and treatment. Univariate analysis of incidence rates (cases/1000 person-years) enabled the identification of significant predictors of risk. Competing risk regression identified predictors of pneumonitis. **RESULTS:** The cohort included 81,628 patients. Overall, 19.0% developed pneumonitis during any LOT, with a cumulative incidence of 33.7% and 17.0% for patients with a prior history of pneumonitis and those without, respectively. Univariate analyses revealed several factors associated with pneumonitis ( $p < 0.05$ ). While factors varied between LOTs, common factors included male gender, squamous histology, history of diabetes or pneumonitis, EGFR-negative status, monotherapy immunomodulatory drugs, or history of radiation therapy. Multivariable competing risk regression showed that male gender, history of pneumonitis, EGFR-negative status, use of other targeted therapies, use of immunomodulatory drugs, and history of radiation therapy predicted pneumonitis. **CONCLUSION:** Pneumonitis is significantly associated with NSCLC treatment. Knowledge of its predictors identified in this study may help devise strategies to mitigate its impact, enhancing treatment adherence and improving outcomes.

**[Determining Risk Factors Associated with Depression and Anxiety in Young Lung Cancer Patients: A Novel Optimization Algorithm](#)** Medicina (Kaunas). 2021 Apr 1;57(4):340. doi: 10.3390/medicina57040340 Yu-Wei Fang 1 2 , Chieh-Yu Liu 3 4

**BACKGROUND AND OBJECTIVES:** Identifying risk factors associated with psychiatrist-confirmed anxiety and depression among young lung cancer patients is very difficult because the incidence and prevalence rates are obviously lower than in middle-aged or elderly patients. Due to the nature of these

rare events, logistic regression may not successfully identify risk factors. Therefore, this study aimed to propose a novel algorithm for solving this problem. **MATERIALS AND METHODS:** A total of 1022 young lung cancer patients (aged 20-39 years) were selected from the National Health Insurance Research Database in Taiwan. A novel algorithm that incorporated a k-means clustering method with v-fold cross-validation into multiple correspondence analyses was proposed to optimally determine the risk factors associated with the depression and anxiety of young lung cancer patients. **RESULTS:** Five clusters were optimally determined by the novel algorithm proposed in this study. **CONCLUSIONS:** The novel Multiple Correspondence Analysis-k-means (MCA-k-means) clustering algorithm in this study successfully identified risk factors associated with anxiety and depression, which are considered rare events in young patients with lung cancer. The clinical implications of this study suggest that psychiatrists need to be involved at the early stage of initial diagnose with lung cancer for young patients and provide adequate prescriptions of antipsychotic medications for young patients with lung cancer.

[Role of myokines and osteokines in cancer cachexia](#) Exp Biol Med (Maywood). 2021 Apr 25;15353702211009213. doi: 10.1177/15353702211009213. Online ahead of print. Fabrizio Pin 1 , Lynda F Bonewald 1 2 3 , Andrea Bonetto 1 2 3 4 5

Cancer-induced muscle wasting, i.e. cachexia, is associated with different types of cancer such as pancreatic, colorectal, lung, liver, gastric and esophageal. Cachexia affects prognosis and survival in cancer, and it is estimated that it will be the ultimate cause of death for up to 30% of cancer patients. Musculoskeletal alterations are known hallmarks of cancer cachexia, with skeletal muscle atrophy and weakness as the most studied. Recent evidence has shed light on the presence of bone loss in cachectic patients, even in the absence of bone-metastatic disease. In particular, we and others have shown that muscle and bone communicate by exchanging paracrine and endocrine factors, known as myokines and osteokines. This review will focus on describing the role of the most studied myokines, such as myostatin, irisin, the muscle metabolite  $\beta$ -aminoisobutyric acid, BAIBA, and IL-6, and osteokines, including TGF- $\beta$ , osteocalcin, sclerostin, RANKL, PTHrP, FGF23, and the lipid mediator, PGE2 during cancer-induced cachexia. The interplay of muscle and bone factors, together with tumor-derived soluble factors, characterizes a complex clinical scenario in which musculoskeletal alterations are amongst the most debilitating features. Understanding and targeting the "secretome" of cachectic patients will likely represent a promising strategy to preserve bone and muscle during cancer cachexia thereby enhancing recovery.

[Variation in Use of High-Cost Technologies for Palliative Radiation Therapy by Radiation Oncologists](#) J Natl Compr Canc Netw. 2021 Feb 12;19(4):421-431. doi: 10.6004/jnccn.2020.7633. Print 2021 Apr. Aileen B Chen 1 , Jiangong Niu 1 , Angel M Cronin 2 , Ya-Chen Tina Shih 1 , Sharon Giordano 1 , Deborah Schrag 2

**BACKGROUND:** Understanding the sources of variation in the use of high-cost technologies is important for developing effective strategies to control costs of care. Palliative radiation therapy (RT) is a discretionary treatment and its use may vary based on patient and clinician factors. **METHODS:** Using data from the SEER-Medicare linked database, we identified patients diagnosed with metastatic lung, prostate, breast, and colorectal cancers in 2010 through 2015 who received RT, and the radiation oncologists who treated them. The costs of radiation services for each patient over a 90-day episode were calculated, and radiation oncologists were assigned to cost quintiles. The use of advanced technologies (eg, intensity-modulated radiation, stereotactic RT) and the number of RT treatments (eg, any site, bone only) were identified. Multivariable random-effects models were constructed to estimate the proportion of variation in the use of advanced technologies and extended fractionation (>10 fractions) that could be explained by patient fixed effects versus physician random effects. **RESULTS:** We identified 37,361 patients with metastatic lung cancer, 3,684 with metastatic breast cancer, 5,323 with metastatic prostate

cancer, and 8,726 with metastatic colorectal cancer, with 34%, 27%, 22%, and 9% receiving RT within the first year, respectively. The use of advanced technologies and extended fractionation was associated with higher costs of care. Compared with the patient case-mix, physician variation accounted for a larger proportion of the variation in the use of advanced technologies for palliative RT and the use of extended fractionation. **CONCLUSIONS:** Differences in radiation oncologists' practice and choices, rather than differences in patient case-mix, accounted for a greater proportion of the variation in the use of advanced technologies and high-cost radiation services.

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## COMPLEMENTARY & ALTERNATIVE THERAPY

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[Phase I Study of Muscadine Grape Extract for Patients With Advanced Cancer](#) Am J Clin Oncol. 2021 Apr 19. doi: 10.1097/COC.0000000000000814. Online ahead of print. Rhonda L Bitting<sup>1</sup>, Janet A Tooze, Scott Isom, et al.

**OBJECTIVE:** Preclinical studies with muscadine grape extract (MGE) show antitumor activity and decreased systemic inflammation. This phase I study (NCT02583269) assessed safety and tolerability of a proprietary MGE preparation in patients with advanced solid tumors. **METHODS:** Patients with metastatic or unresectable cancers who were progressing on standard therapies were assigned to MGE in a standard 3+3 design. Five dose levels were tested (320 to 1600 mg total phenolics/d). Safety and maximum-tolerated dose were assessed after 4 weeks. Patients were evaluated for response at 8 weeks and continued on MGE if clinically stable. Secondary outcomes were response, survival, adherence, fatigue, and quality of life (QOL). **RESULTS:** In total, 23 patients (lung, n=7; gastrointestinal, n=7; genitourinary, n=6; other, n=3) received MGE capsules by mouth twice daily. The cohort [median age 72 years, 48% Eastern Cooperative Oncology Group (ECOG) 2] was heavily pretreated. After 4 weeks on MGE, possibly attributable adverse events grade 2 or higher were fatigue (n=1), decreased lymphocyte count (n=1), and constipation (n=2), including 1 dose-limiting toxicity for grade 3 constipation. Maximum-tolerated dose was not reached. No partial responses were observed. Median time on therapy was 8 weeks, with 29% of patients treated beyond 16 weeks and a median overall survival of 7.2 months. QOL and fatigue levels were stable from baseline to 8 weeks. Higher MGE dose was correlated with improvement in self-reported physical well-being QOL at 8 weeks (r=0.6; P=0.04). **CONCLUSIONS:** MGE is safe and well-tolerated in heavily pretreated and older cancer patients. The potential anticancer properties and the effects of MGE on physical well-being and QOL metrics will be evaluated in future studies.

[A Combined Phytochemistry and Network Pharmacology Approach to Reveal Potential Anti-NSCLC Effective Substances and Mechanisms in Marsdenia tenacissima \(Roxb.\) Moon \(Stem\)](#)

Front Pharmacol. 2021 Apr 29;12:518406. doi: 10.3389/fphar.2021.518406. eCollection 2021.

Pei Liu<sup>1 2</sup>, Dong-Wei Xu<sup>1 2</sup>, Run-Tian Li<sup>1 2</sup>, et al.

*Marsdenia tenacissima* Caulis is a traditional Chinese medicine, named Tongguanteng (TGT), that is often used for the adjuvant treatment of cancer. In our previous study, we reported that an ethyl acetate extract of TGT had inhibitory effects against adenocarcinoma A549 cells growth. To identify the components of TGT with anti-tumor activity and to elucidate their underlying mechanisms of action, we developed a technique for isolating compounds, which was then followed by cytotoxicity screening, network pharmacology analysis, and cellular and molecular experiments. We isolated a total of 19 compounds from a TGT ethyl acetate extract. Two novel steroidal saponins were assessed using an ultra-performance liquid chromatography-photodiode array coupled with quadrupole time-of-flight mass (UPLC-ESI-Q/TOF-MS). Then, we screened these constituents for anti-cancer activity against non-small cell lung cancer (NSCLC) in vitro and obtained six target compounds. Furthermore, a compound-target-pathway network of these six bioactive ingredients was constructed to elucidate the potential pathways



that controlled anticancer effects. Approximately 205 putative targets that were associated with TGT, as well as 270 putative targets that were related to NSCLC, were obtained from online databases and target prediction software. Protein-protein interaction networks for drugs as well as disease putative targets were generated, and 18 candidate targets were detected based on topological features. In addition, pathway enrichment analysis was performed to identify related pathways, including PI3K/AKT, VEGF, and EGFR tyrosine kinase inhibitor resistance, which are all related to metabolic processes and intrinsic apoptotic pathways involving reactive oxygen species (ROS). Then, various cellular experiments were conducted to validate drug-target mechanisms that had been predicted using network pharmacology analysis. The experimental results showed the four C21 steroidal saponins could upregulate Bax and downregulate Bcl-2 expression, thereby changing the mitochondrial membrane potential, producing ROS, and releasing cytochrome C, which finally activated caspase-3, caspase-9, and caspase-8, all of which induced apoptosis in A549 cells. In addition, these components also downregulated the expression of MMP-2 and MMP-9 proteins, further weakening their degradation of extracellular matrix components and type IV collagen, and inhibiting the migration and invasion of A549 cells. Our study elucidated the chemical composition and underlying anti-tumor mechanism of TGT, which may be utilized in the treatment of lung cancer.

[Clinical observation of Yiqi Qingdu prescription on the treatment of intermediate-stage and advanced non-small-cell lung cancer](#) J Tradit Chin Med. 2021 Apr;41(2):308-315.

Qijun Liang 1 , Xiaoling Tang 2 , Jiong Yu 3 , Monian Xiong 3 , Huifang Zhu 4 , Linkai Xiong 5 , Ru Zeng 4 , Peiwen Yu 4

**OBJECTIVE:** To observe the effects of the Yiqi Qingdu prescription () on intermediate-stage and advanced non-small-cell lung cancer (NSCLC). **METHODS:** In total, 300 patients with intermediate-stage or advanced NSCLC were randomly and equally divided into three groups using computer-generated random numbers as follows: Western medicine (WM), Chinese medicine (CM), and integrated Traditional Chinese and Western Medicine (IM). After 3 months of treatment, the overall response rate (ORR); disease control rate (DCR); symptom score (SS); Karnofsky performance status (KPS); adverse event score; counts of CD3 + , CD4 + , and CD8 + cells; CD4 + /CD8 + ratio; and carcinoembryonic antigen (CEA) level were compared among the groups. **RESULTS:** The ORRs were 30.36% , 20.24% , and 7.87% in the IM, CM, and WM groups, respectively, whereas the DCRs were 85%, 75%, and 73%, respectively. Compared to the CM group, the ORR was significantly higher in the WM and IM groups, whereas the DCR was significantly higher in the IM group (all  $P < 0.05$ ). SS was obviously higher in the WM group than in the other two groups (both  $P < 0.01$ ). KPS was significantly lower in the WM group after treatment ( $P = 0.005$ ). The mean number of adverse events was significantly lower in the CM ( $2.2 \pm 1.3$ ) and IM ( $2.4 \pm 1.3$ ) groups than in the WM group ( $4.6 \pm 1.7$ , both  $P < 0.05$ ). CD3 + cell counts were significantly decreased in the WM group ( $P = 0.031$ ). In the IM group, CD8+ cell counts were increased after treatment, whereas the CD4 + /CD8 + ratio was decreased (both  $P < 0.01$ ). Compared with the WM group, CD3 + ( $P = 0.01$ ), CD4 + ( $P = 0.044$ ), and CD8 + ( $P = 0.009$ ) cell counts were significantly higher in the IM group, whereas the CD4+ /CD8+ ratio was significantly lower ( $P = 0.011$ ). Relative to the CM group, CD8 + cell counts were significantly higher ( $P = 0.001$ ) and the CD4+ /CD8+ ratio was significantly lower in the IM group ( $P = 0.001$ ). CEA levels were significantly increased in the CM group ( $P = 0.023$ ). **CONCLUSION:** The Yiqi Qingdu prescription can improve the outcomes of WM in patients with NSCLC.

[Nutrient supplements from selected botanicals mediated immune modulation of the tumor microenvironment and antitumor mechanism](#) Cancer Immunol Immunother. 2021 Apr 20. doi:

10.1007/s00262-021-02927-2. Online ahead of print. Hui-Ming Chen 1 2 3 , Linus Sun 4 , Ping-Ying Pan 1 2 3 , Lu-Hai Wang 5 , Shu-Hsia Chen 6 7 8 9

Specific extracts of selected vegetables (SV) have been shown to benefit the survival of stage IIIb/IV non-small cell lung cancer patients in phase I/II studies and is currently in a phase III trial. However, the underlying mechanism of SV-mediated antitumor immune responses has not been elucidated. Our results indicate that SV modulated the NK and adoptive T cell immune responses in antitumor efficacy. Furthermore, antitumor effects of SV were also mediated by innate myeloid cell function, which requires both TLR and  $\beta$ -glucan signaling in a MyD88/TRIF and Dectin-1-dependent manner, respectively. Additionally, SV treatment reduced granulocytic myeloid-derived suppressor cell (MDSC) infiltration into the tumor and limited monocytic MDSC toward the M2-like functional phenotype. Importantly, SV treatment enhanced antigen-specific immune responses by augmenting the activation of antigen-specific TH1/TH17 cells in secondary lymphoid organs and proliferative response, as well as by reducing the Treg population in the tumor microenvironment, which was driven by SV-primed activated M-MDSC. Our results support the idea that SV can subvert immune-tolerance state in the tumor microenvironment and inhibit tumor growth. The present study suggests that features, such as easy accessibility, favorable clinical efficacy, no detectable side effects and satisfactory safety make SV a feasible, appealing and convincing adjuvant therapy for the treatment of cancer patients and prevent tumor recurrence and/or metastases.

**[The Use of Traditional Chinese Medicine in Relieving EGFR-TKI-Associated Diarrhea Based on Network Pharmacology and Data Mining](#)** Evid Based Complement Alternat Med. 2021 Apr

1;2021:5530898. doi: 10.1155/2021/5530898. eCollection 2021. Shuaihang Hu <sup>1 2</sup>, Wenchao Dan <sup>1 2</sup>, Jinlei Liu <sup>1 2</sup>, Peng Ha <sup>3</sup>, Tong Zhou <sup>1</sup>, Xinyuan Guo <sup>4</sup>, Wei Hou <sup>1</sup>

In this study, the role of traditional Chinese medicine (TCM) in relieving epidermal growth factor receptor-tyrosine kinase inhibitor- (EGFR-TKI-) associated diarrhea was discussed by network pharmacology and data mining. Prediction of drug targets by introducing the EGFR-TKI molecular structures into the SwissTargetPrediction platform and diarrhea-related targets in the DrugBank, GeneCards, DisGeNET, and OMIM databases were obtained. Compounds in the drug-disease target intersection were screened by absorption, distribution, metabolism, and excretion parameters and Lipinski's rule in Traditional Chinese Medicine Systems Pharmacology. TCM-containing compounds were selected, and information on the property, taste, and meridian tropism of these TCMs was summarized and analyzed. A target-compound-TCM network diagram was constructed, and core targets, compounds, and TCMs were selected. The core targets and components were docked by AutoDock Vina (Version 1.1.2) to explore the target combinations of related compounds and evaluate the docking activity of related targets and compounds. Twenty-three potential therapeutic TCM targets for the treatment of EGFR-TKI-related diarrhea were obtained. There were 339 compounds acting on potential therapeutic targets, involving a total of 402 TCMs. The results of molecular docking showed good binding between the core targets and compounds, and the binding between the core targets and compounds was similar to that of the core target and the recommended drug loperamide. TCMs have multitarget characteristics and are present in a variety of compounds used for relieving EGFR-TKI-associated diarrhea. Antitumor activity and the efficacy of alleviating diarrhea are the pharmacological basis of combining TCMs with EGFR-TKI in the treatment of non-small-cell lung cancer. The core targets, compounds, and TCMs can provide data to support experimental and clinical studies on the relief of EGFR-TKI-associated diarrhea in the future.

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**MISCELLANEOUS WORKS**

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**[Cancer Mortality Disparities among Asian American and Native Hawaiian/Pacific Islander Populations in California](#)** Cancer Epidemiol Biomarkers Prev. 2021 Apr 20;cebp.1528.2020. doi:

10.1158/1055-9965.EPI-20-1528. Online ahead of print. Heidy N Medina <sup>1</sup> , Karen E Callahan <sup>2</sup> , Cyllene R Morris <sup>3</sup> , Caroline A Thompson <sup>4</sup> , Adugna Siweya <sup>2</sup> , Paulo S Pinheiro <sup>5</sup>

**BACKGROUND:** Asian American and Native Hawaiian/Pacific Islanders (AANHPI) are the fastest growing minority in the US. Cancer is the leading cause of death for AANHPIs, despite relatively lower cancer morbidity and mortality. Their recent demographic growth facilitates a detailed identification of AANHPI populations with higher cancer risk. **METHODS:** Age-adjusted, sex-stratified, site-specific cancer mortality rates from California for 2012-2017 were computed for AANHPI groups: Chinese, Filipino, South Asian, Vietnamese, Korean, Japanese, Southeast Asian (i.e., Cambodian, Hmong, Laotian, Thai), and Native Hawaiian and Other Pacific Islander (NHOPI). Regression-derived mortality rate ratios (MRR) were used to compare each AANHPI group to non-Hispanic whites (NHWs). **RESULTS:** AANHPI men and women (total 40,740 deaths) had lower all-sites-combined cancer mortality rates (128.3 and 92.4 per 100,000, respectively) than NHWs (185.3 and 140.6) but higher mortality for nasopharynx, stomach, and liver cancers. Among AANHPIs, both NHOPIs and Southeast Asians had the highest overall rates including for colorectal, lung (men only), and cervical cancers; South Asians had the lowest. NHOPI women had 41% higher overall mortality than NHWs (MRR:1.41;95%CI:1.25-1.58), including for breast (MRR:1.33; 95%CI:1.08-1.65) and markedly higher for endometrial cancer (MRR:3.34; 95%CI:2.53-4.42). **CONCLUSIONS:** AANHPI populations present with considerable heterogeneous cancer mortality patterns. Heightened mortality for infection, obesity, and tobacco-related cancers in Southeast Asians and NHOPI populations highlight the need for differentiated priorities and public health interventions among specific AANHPI populations. **IMPACT:** Not all AANHPIs have favorable cancer profiles. It is imperative to expand the focus on the currently understudied populations that bear a disproportionate cancer burden.

[What Does a Cardio-oncology Service Offer to the Oncologist and the Haematologist?](#) Clin Oncol (R Coll Radiol). 2021 Apr 5;S0936-6555(21)00103-5. doi: 10.1016/j.clon.2021.03.012. Online ahead of print. M S Andres <sup>1</sup> , J Pan <sup>2</sup> , A R Lyon <sup>3</sup>

Cardio-oncology is an emerging subspecialty arising from the need for multidisciplinary collaboration to address the increasing prominence of cardiovascular disease (CVD) among cancer patients. This overview outlines the case for establishing cardio-oncology services and defines the ways in which these services benefit cancer patients. The primary objective of cardio-oncology is to manage CVDs in order to allow cancer patients to complete the best cancer treatments safely and with minimal interruption. In the decades since the first discovery of heart failure induced by anthracycline chemotherapy, both cardiovascular and oncological science have advanced considerably. Cardio-oncology services aim to bring together expertise from these two fast moving fields in order to provide optimal evidence-based care for cancer patients with CVDs. Here we discuss the basis of cardio-oncology services by presenting their rationale and key components, as well as their essential roles in education, training and research. At each stage of the cancer care pathway, a cardio-oncology service can add value by ensuring cancer patients have timely access to specialist care backed up by cutting edge diagnostic tools and treatment options, as well as holistic supports. We highlight areas of recent and upcoming developments in the field that are likely to change established clinical practice. Improved cardiac imaging modalities can detect chemotherapy-related cardiac dysfunction earlier and are also essential for the prompt diagnosis of an expanding range of cardiovascular effects complicating newer cancer therapeutics, such as immune checkpoint inhibitors and other targeted therapies. Modern cancer therapy has dramatically improved cancer survival and as such CVD is becoming one of the principal determinants of overall outcome for cancer patients. A dedicated cardio-oncology service can facilitate the optimisation of cardiovascular treatment and enable the completion of cancer therapy. A multidisciplinary collaborative approach is key to achieving these objectives.

[Beliefs About the Health Effects of Smoking Among Adults in the United States](#) Health Educ Behav. 2021 Apr 17;10901981211004136. doi: 10.1177/10901981211004136. Online ahead of print. Sarah D Mills 1 2 , Christopher A Wiesen 3

The majority of U.S. adults believe that smoking is a cause of lung cancer, but research suggests that the percentage of adults who believe smoking causes other types of cancers and chronic disease is lower. This study examines the correlates of beliefs about several established health effects of smoking in a nationally representative sample of U.S. adults. Data for this study come from Wave 4 of the Population Assessment of Tobacco and Health Study conducted from December 2016 to January 2018. Participants responded to questions assessing their beliefs about the health effects of smoking. Logistic regression models were used to examine the relationship between beliefs about the health effects of smoking and sociodemographic characteristics (smoker status, age, sex, education, race/ethnicity), exposure to antitobacco campaigns, smokers' health, and nicotine dependence. The percentage of U.S. adults who endorsed a health effect can be caused from smoking ranged from 56.4% for blindness to 97.4% for lung disease. Respondents who were older, less educated, current or former smokers, and had less exposure to antitobacco campaigns were generally less likely ( $p < .05$ ) to endorse that an established health effect was caused by smoking. Smokers with lower nicotine dependence and worse health were generally more likely ( $p < .05$ ) to endorse that an established health effect was caused by smoking. In summary, knowledge about the health effects of smoking varies across health conditions. Public health would benefit from campaigns targeting segments of the population with less knowledge about the health effects of smoking.

[Population-based estimates of survival among elderly patients with brain metastases](#) Neuro Oncol. 2021 Apr 12;23(4):661-676. doi: 10.1093/neuonc/noaa233. Nayan Lamba 1 , Rachel Brigell Kearney 1 , Paul J Catalano 2 , Michael J Hassett 3 , Patrick Y Wen 4 , Daphne A Haas-Kogan 1 , Ayal A Aizer 1

**BACKGROUND:** Prognostic estimates for patients with brain metastases (BM) stem from younger, healthier patients enrolled in clinical trials or databases from academic centers. We characterized population-level prognosis in elderly patients with BM. **METHODS:** Using Surveillance, Epidemiology, and End Results (SEER)-Medicare data, we identified 9882 patients  $\geq 65$  years old with BM secondary to lung, breast, skin, kidney, esophageal, colorectal, and ovarian primaries between 2014 and 2016. Survival was assessed by primary site and evaluated with Cox regression. **RESULTS:** In total, 2765 versus 7117 patients were diagnosed with BM at primary cancer diagnosis (synchronous BM, median survival = 2.9 mo) versus thereafter (metachronous BM, median survival = 3.4 mo), respectively. Median survival for all primary sites was  $\leq 4$  months, except ovarian cancer (7.5 mo). Patients with non-small-cell lung cancer (NSCLC) receiving epidermal growth factor receptor (EGFR)- or anaplastic lymphoma kinase (ALK)-based therapy for synchronous BM displayed notably better median survival at 12.5 and 20.1 months, respectively, versus 2.8 months exhibited by other patients with NSCLC; survival estimates in melanoma patients based on receipt of BRAF/MEK therapy versus not were 6.7 and 2.8 months, respectively. On multivariable regression, older age, greater comorbidity, and type of managing hospital were associated with poorer survival; female sex, higher median household income, and use of brain-directed stereotactic radiation, neurosurgical resection, or systemic therapy (versus brain-directed non-stereotactic radiation) were associated with improved survival (all  $P < 0.05$ ). **CONCLUSIONS:** Elderly patients with BM have a poorer prognosis than suggested by prior algorithms. If prognosis is driven by systemic and not intracranial disease, brain-directed therapy with potential for significant toxicity should be utilized cautiously.

[Experiences of Inuit in Canada who travel from remote settings for cancer care and impacts on decision making](#) BMC Health Serv Res. 2021 Apr 13;21(1):328. doi: 10.1186/s12913-021-06303-9. Janet Jull 1 , Amanda J Sheppard 2 , et al. .

**BACKGROUND:** Inuit experience the highest cancer mortality rates from lung cancer in the world with increasing rates of other cancers in addition to other significant health burdens. Inuit who live in remote areas must often travel thousands of kilometers to large urban centres in southern Canada and negotiate complex and sometimes unwelcoming health care systems. There is an urgent need to improve Inuit access to and use of health care. Our study objective was to understand the experiences of Inuit in Canada who travel from a remote to an urban setting for cancer care, and the impacts on their opportunities to participate in decisions during their journey to receive cancer care. **METHODS:** We are an interdisciplinary team of Steering Committee and researcher partners ("the team") from Inuit-led and/or -specific organizations that span Nunavut and the Ontario cancer health systems. Guided by Inuit societal values, we used an integrated knowledge translation (KT) approach with qualitative methods. We conducted semi-structured interviews with Inuit participants and used process mapping and thematic analysis. **RESULTS:** We mapped the journey to receive cancer care and related the findings of client (n = 8) and medical escort (n = 6) ("participant") interviews in four themes: 1) It is hard to take part in decisions about getting health care; 2) No one explains the decisions you will need to make; 3) There is a duty to make decisions that support family and community; 4) The lack of knowledge impacts opportunities to engage in decision making. Participants described themselves as directed, with little or no support, and seeking opportunities to collaborate with others on the journey to receive cancer care. **CONCLUSIONS:** We describe the journey to receive cancer care as a "decision chain" which can be described as a series of events that lead to receiving cancer care. We identify points in the decision chain that could better prepare Inuit to participate in decisions related to their cancer care. We propose that there are opportunities to build further health care system capacity to support Inuit and enable their participation in decisions related to their cancer care while upholding and incorporating Inuit knowledge.

[Line of therapy and patient preferences regarding lung cancer treatment: a discrete-choice experiment](#) *Curr Med Res Opin.* 2021 Apr;37(4):643-653. doi: 10.1080/03007995.2021.1888707. Epub 2021 Mar 1. Sarah Janse 1 , Ellen Janssen 2 , Tanya Huwig 1 , Upal Basu Roy 3 , Andrea Ferris 3 , Carolyn J Presley 4 , John F P Bridges 1 5

**OBJECTIVE:** A growing literature on patient preferences informs decisions in research, regulatory science, and value assessment, but few studies have explored how preferences vary across patients with differing treatment experience. We sought to quantify patient preferences for the benefits and risks of lung cancer treatment and test how preferences differed by line of therapy (LOT). **METHODS:** Preferences were elicited using a discrete choice experiment (DCE) following rigorous patient and stakeholder engagement. The DCE spanned five attributes (each with three levels): progression-free survival (PFS), short-term side effects, long-term side effects, risk of developing late-onset side effects, and mode of administration (MOA) - each defined across 3 relevant levels. A D-efficient design was used to generate 3 survey blocks of 9 paired-profile choice tasks each and respondents were asked which profile they preferred and then if they preferred to have no treatment (opt-out). A mixed logit model, controlling for opt-out, was used to estimate preferences. Preferences and trade-offs between PFS and other attributes were compared across two groups: those receiving  $\leq 1$  LOT and those receiving  $\geq 2$  LOT. **RESULTS:** Of the 466 participants, 42% received  $\leq 1$  LOT and 58% received  $\geq 2$  LOT. Stated preferences differed between the groups overall ( $p < .001$ ) and specifically for 18 months of PFS ( $p < .001$ ), moderate short-term side effects ( $p < .001$ ), no long-term side effects ( $p = .03$ ), and 30% chance of late-onset side effects ( $p = .02$ ). Those receiving differing amounts of LOT were willing to trade different amounts of PFS to change from moderate to mild short-term side effects ( $p < .001$ ), moderate to no ( $p < .001$ ) and mild to no ( $p < .001$ ) long-term side effects. There were also differing amounts of tradeoff acceptable between the groups for a 10% decrease in risk of late-onset side effects ( $p = .016$ ), a decrease in MOA from infusion every 3 weeks to pills taken daily at any time ( $p = .005$ ) and from pills taken daily without food to pills taken daily at any time ( $p < .001$ ). **CONCLUSION:** We demonstrate differences in preferences based on experience with

LOT, suggesting that patient treatment experience may have an impact on their preferences. As patient preference data become an important component of treatment decision making, preference differences should be considered when recommending therapies at different stages in the treatment journey. Understanding patient preferences regarding treatment decisions is essential to informing shared decision-making and ensuring treatment plans are consistent with patients' goals.

[Dynamic Management of Lung Cancer Care During Surging COVID-19](#) *Front Surg.* 2021 Apr 7;8:663364. doi: 10.3389/fsurg.2021.663364. eCollection 2021. Annie Wang 1 , Stephanie H Chang 2 , Eric J Kim 3 , Jamie L Bessich 4 , Joshua K Sabari 4 , Benjamin Cooper 5 , Travis C Geraci 2 , Robert J Cerfolio 2

Management of patients with lung cancer continues to be challenging during the COVID-19 pandemic, due to the increased risk of complications in this subset of patients. During the COVID-19 surge in New York City, New York University Langone Health adopted triage strategies to help with care for lung cancer patients, with good surgical outcomes and no transmission of COVID-19 to patients or healthcare workers. Here, we will review current recommendations regarding screening and management of lung cancer patients during both a non-surge phase and surge phase of COVID-19.

[Understanding the patient journey to diagnosis of lung cancer](#) *BMC Cancer.* 2021 Apr 14;21(1):402. doi: 10.1186/s12885-021-08067-1. Yichen Zhang 1 , Michael J Simoff 2 , David Ost 3 , Oliver J Wagner 4 , James Lavin 4 , Beth Nauman 5 , Mei-Chin Hsieh 6 , Xiao-Cheng Wu 6 , Brian Pettiford 7 , Lizheng Shi 1

**OBJECTIVE:** This research describes the clinical pathway and characteristics of two cohorts of patients. The first cohort consists of patients with a confirmed diagnosis of lung cancer while the second consists of patients with a solitary pulmonary nodule (SPN) and no evidence of lung cancer. Linked data from an electronic medical record and the Louisiana Tumor Registry were used in this investigation.

**MATERIALS AND METHODS:** REACHnet is one of 9 clinical research networks (CRNs) in PCORnet®, the National Patient-Centered Clinical Research Network and includes electronic health records for over 8 million patients from multiple partner health systems. Data from Ochsner Health System and Tulane Medical Center were linked to Louisiana Tumor Registry (LTR), a statewide population-based cancer registry, for analysis of patient's clinical pathways between July 2013 and 2017. Patient characteristics and health services utilization rates by cancer stage were reported as frequency distributions. The Kaplan-Meier product limit method was used to estimate the time from index date to diagnosis by stage in lung cancer cohort. **RESULTS:** A total of 30,559 potentially eligible patients were identified and 2929 (9.58%) had primary lung cancer. Of these, 1496 (51.1%) were documented in LTR and their clinical pathway to diagnosis was further studied. Time to diagnosis varied significantly by cancer stage. A total of 24,140 patients with an SPN were identified in REACHnet and 15,978 (66.6%) had documented follow up care for 1 year. 1612 (10%) had no evidence of any work up for their SPN. The remaining 14,366 had some evidence of follow up, primarily office visits and additional chest imaging. **CONCLUSION:** In both cohorts multiple biopsies were evident in the clinical pathway. Despite clinical workup, 70% of patients in the lung cancer cohort had stage III or IV disease. In the SPN cohort, only 66% were identified as receiving a diagnostic work-up.

[Coronavirus 2019 Infectious Disease Epidemic: Where We Are, What Can Be Done and Hope For](#)

*J Thorac Oncol.* 2021 Apr;16(4):546-571. doi: 10.1016/j.jtho.2020.12.014. Epub 2021 Jan 7. Michele Carbone 1 , John Lednický 2 , Shu-Yuan Xiao 3 , Mario Venditti 4 , Enrico Bucci 5  
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spreads mainly by means of aerosols (microdroplets) in enclosed environments, especially those in which temperature and humidity are regulated by means of air-conditioning. About 30% of individuals infected with SARS-CoV-2 develop

coronavirus disease 2019 (COVID-19) disease. Among them, approximately 25% require hospitalization. In medicine, cases are identified as those who become ill. During this pandemic, cases have been identified as those with a positive SARS-CoV-2 polymerase chain reaction test, including approximately 70% who were asymptomatic-this has caused unnecessary anxiety. Individuals more than 65 years old, those affected by obesity, diabetes, asthma, or are immune-depressed owing to cancer and other conditions, are at a higher risk of hospitalization and of dying of COVID-19. Healthy individuals younger than 40 years very rarely die of COVID-19. Estimates of the COVID-19 mortality rate vary because the definition of COVID-19-related deaths varies. Belgium has the highest death rate at 154.9 per 100,000 persons, because it includes anyone who died with symptoms compatible with COVID-19, even those never tested for SARS-CoV-2. The United States includes all patients who died with a positive test, whether they died because of, or with, SARS-CoV-2. Countries that include only patients in which COVID-19 was the main cause of death, rather than a cofactor, have lower death rates. Numerous therapies are being developed, and rapid improvements are anticipated. Because of disinformation, only approximately 50% of the U.S. population plans to receive a COVID-19 vaccine. By sharing accurate information, physicians, health professionals, and scientists play a key role in addressing myths and anxiety, help public health officials enact measures to decrease infections, and provide the best care for those who become sick. In this article, we discuss these issues.