



Caring Ambassadors Lung Cancer Program

Literature Review, April 2022

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SCREENING, COMPREHENSIVE BIOMARKER TESTING, DIAGNOSIS AND STAGING

[Psychological Traits and the Persuasiveness of Lung Cancer Screening Health Messages](#) Ann Thorac Surg. 2022 Apr;113(4):1341-1347. doi: 10.1016/j.athoracsur.2021.04.047. Epub 2021 May 3. John I Monu 1, Chethana Achar 2, Douglas E Wood 1, David R Flum 1, Nidhi Agrawal 3, Farhood Farjah 4

BACKGROUND: Lung cancer screening remains underused despite its proven mortality benefit. Health systems have attempted to increase screening awareness through advertising. Psychological theories suggest that construal level (a personal orientation toward the big picture or the details) and regulatory focus (goals emphasizing acquisition of a good or avoidance of a bad outcome) play a key role in health advertising effectiveness. These theories have not been examined in a screen-eligible population.

METHODS: Using Amazon's crowdsourcing platform, Mechanical Turk, we identified screen-eligible individuals based on US Preventive Services Task Force criteria. We randomly assigned participants to see 1 of 4 screening advertisement images in a 2 (construal level: high vs low) × 2 (regulatory focus: promotion vs prevention) between-subjects experimental design. We assessed willingness to undergo screening after the advertisement.

RESULTS: One hundred ninety-one individuals responded to our study invitation (mean age, 61 years). We found that the high construal/promotion focus image led to a greater willingness to screen compared with images representing other psychological states ($P = .04$). Regarding the personality traits of our respondents, high construal/promotion focus was the most prevalent (40%) trait combination, whereas low construal/prevention focus was the least prevalent (17%).

CONCLUSIONS: The psychological focus of health-related messages affects an individual's willingness to undergo lung cancer screening. Individuals eligible for lung cancer screening are more persuaded by "big picture" messages describing the benefits of screening. Health systems may use this knowledge to design more effective patient-facing communications that lead to higher rates of screening.

[Different Prognostic Values of Dual-Time-Point FDG PET/CT Imaging Features According to Treatment Modality in Patients with Non-Small Cell Lung Cancer](#) Tomography. 2022 Apr 8;8(2):1066-1078. doi: 10.3390/tomography8020087. Su Jin Jang 1, Jeong Won Lee 2, Ji-Hyun Lee 3, In Young Jo 4, Sang Mi Lee 5

This study was aimed to investigate whether dual-time-point F-18 fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT) imaging features had different prognostic values according to the treatment modality in patients with non-small cell lung cancer (NSCLC). We retrospectively reviewed 121 NSCLC patients with surgical resection (surgery group) and 69 NSCLC patients with chemotherapy and/or radiotherapy (CRT group), who underwent pretreatment dual-time-point FDG PET/CT. The maximum standardized uptake value (SUV), metabolic tumor volume (MTV), total lesion glycolysis (TLG), SUV histogram entropy of primary cancer, and the percent changes in these parameters (Δ parameters) were measured. In multivariate analysis, MTV, TLG, and entropy on both early and delayed PET/CT scans were significantly associated with progression-free survival (PFS) in the surgery group, but all Δ parameters failed to show a significant association. In the CRT group, TLG on the early PET, maximum SUV on the delayed PET, Δ MTV, and Δ TLG were significant independent predictors for PFS. In the surgery group, patients with high values of MTV, TLG, and entropy had worse survival, whereas, in the CRT group, patients with high values of Δ MTV and Δ TLG had better survival. Dual-time-point FDG PET/CT parameters showed different prognostic values between the surgery and CRT groups of NSCLC patients.

Variation in targetable genomic alterations in non-small cell lung cancer by genetic ancestry, sex, smoking history, and histology Genome Med. 2022 Apr 15;14(1):39. doi: 10.1186/s13073-022-01041-x. Elio Adib # 1 2 , Amin H Nassar # 1 2 , Sarah Abou Alaiwi 1 2 , Stefan Groha 3 4 , Elie W Akl 1 , Lynette M Sholl 5 , Kesi S Michael 6 , Mark M Awad 6 , Pasi A Jänne 6 , Alexander Gusev 3 4 , David J Kwiatkowski 7

BACKGROUND: Genomic alterations in 8 genes are now the targets of FDA-approved therapeutics in non-small cell lung cancer (NSCLC), but their distribution according to genetic ancestry, sex, histology, and smoking is not well established. **METHODS:** Using multi-institutional genetic testing data from GENIE, we characterize the distribution of targetable genomic alterations in 8 genes among 8675 patients with NSCLC (discovery cohort: DFCI, N = 3115; validation cohort: Duke, Memorial Sloan Kettering Cancer Center, Vanderbilt, N = 5560). For the discovery cohort, we impute genetic ancestry from tumor-only sequencing and identify differences in the frequency of targetable alterations across ancestral groups, smoking pack-years, and histologic subtypes. **RESULTS:** We identified variation in the prevalence of KRASG12C, sensitizing EGFR mutations, MET alterations, ALK, and ROS1 fusions according to the number of smoking pack-years. A novel method for computing continental (African, Asian, European) and Ashkenazi Jewish ancestries from panel sequencing enables quantitative analysis of the correlation between ancestry and mutation rates. This analysis identifies a correlation between Asian ancestry and EGFR mutations and an anti-correlation between Asian ancestry and KRASG12C mutation. It uncovers 2.7-fold enrichment for MET exon 14 skipping mutations and amplifications in patients of Ashkenazi Jewish ancestry. Among never/light smokers, targetable alterations in LUAD are significantly enriched in those with Asian (80%) versus African (49%) and European (55%) ancestry. Finally, we show that 5% of patients with squamous cell carcinoma (LUSC) and 17% of patients with large cell carcinoma (LCLC) harbor targetable alterations. **CONCLUSIONS:** Among patients with NSCLC, there was significant variability in the prevalence of targetable genomic alterations according to genetic ancestry, histology, and smoking. Patients with LUSC and LCLC have 5% rates of targetable alterations supporting consideration for sequencing in those subtypes.

Inaccuracies in electronic health records smoking data and a potential approach to address resulting underestimation in determining lung cancer screening eligibility J Am Med Inform Assoc. 2022 Apr 13;29(5):779-788. doi: 10.1093/jamia/ocac020. Polina V Kukhareva 1 , Tanner J Caverly 2 3 4 , Haojia Li 5 , et al.

OBJECTIVE: The US Preventive Services Task Force (USPSTF) requires the estimation of lifetime pack-years to determine lung cancer screening eligibility. Leading electronic health record (EHR) vendors calculate pack-years using only the most recently recorded smoking data. The objective was to characterize EHR smoking data issues and to propose an approach to addressing these issues using longitudinal smoking data. **MATERIALS AND METHODS:** In this cross-sectional study, we evaluated 16 874 current or former smokers who met USPSTF age criteria for screening (50-80 years old), had no prior lung cancer diagnosis, and were seen in 2020 at an academic health system using the Epic® EHR. We described and quantified issues in the smoking data. We then estimated how many additional potentially eligible patients could be identified using longitudinal data. The approach was verified through manual review of records from 100 subjects. **RESULTS:** Over 80% of evaluated records had inaccuracies, including missing packs-per-day or years-smoked (42.7%), outdated data (25.1%), missing years-quit (17.4%), and a recent change in packs-per-day resulting in inaccurate lifetime pack-years estimation (16.9%). Addressing these issues by using longitudinal data enabled the identification of 49.4% more patients potentially eligible for lung cancer screening ($P < .001$). **DISCUSSION:** Missing, outdated, and inaccurate smoking data in the EHR are important barriers to effective lung cancer screening. Data collection and analysis strategies that reflect changes in smoking habits over time could improve the identification of patients eligible for screening. **CONCLUSION:** The use of longitudinal EHR smoking data could improve lung cancer screening.

[Expanding the Reach of Precision Oncology by Drugging All KRAS Mutants](#) Cancer Discov. 2022 Apr 1;12(4):924-937. doi: 10.1158/2159-8290.CD-21-1331. Marco H Hofmann¹, Daniel Gerlach¹, Sandra Misale², Mark Petronczki¹, Norbert Kraut¹

KRAS is the most frequently mutated oncogene, harboring mutations in approximately one in seven cancers. Allele-specific KRASG12C inhibitors are currently changing the treatment paradigm for patients with KRASG12C-mutated non-small cell lung cancer and colorectal cancer. The success of addressing a previously elusive KRAS allele has fueled drug discovery efforts for all KRAS mutants. Pan-KRAS drugs have the potential to address broad patient populations, including KRASG12D-, KRASG12V-, KRASG13D-, KRASG12R-, and KRASG12A-mutant or KRAS wild-type-amplified cancers, as well as cancers with acquired resistance to KRASG12C inhibitors. Here, we review actively pursued allele-specific and pan-KRAS inhibition strategies and their potential utility. **SIGNIFICANCE:** Mutant-selective KRASG12C inhibitors target a fraction (approximately 13.6%) of all KRAS-driven cancers. A broad arsenal of KRAS drugs is needed to comprehensively conquer KRAS-driven cancers. Conceptually, we foresee two future classes of KRAS medicines: mutant-selective KRAS drugs targeting individual variant alleles and pan-KRAS therapeutics targeting a broad range of KRAS alterations.

[Targeting mutations in cancer](#) J Clin Invest. 2022 Apr 15;132(8):e154943. doi: 10.1172/JCI154943. Michael R Waarts^{1,2,3,4}, Aaron J Stonestrom^{2,3,4,5}, Young C Park^{2,3,4}, Ross L Levine^{2,3,4,5}

Targeted therapies have come to play an increasingly important role in cancer therapy over the past two decades. This success has been made possible in large part by technological advances in sequencing, which have greatly advanced our understanding of the mutational landscape of human cancer and the genetic drivers present in individual tumors. We are rapidly discovering a growing number of mutations that occur in targetable pathways, and thus tumor genetic testing has become an important component in the choice of appropriate therapies. Targeted therapy has dramatically transformed treatment outcomes and disease prognosis in some settings, whereas in other oncologic contexts, targeted approaches have yet to demonstrate considerable clinical efficacy. In this Review, we summarize the current knowledge of targetable mutations that occur in a range of cancers, including hematologic malignancies and solid tumors such as non-small cell lung cancer and breast cancer. We outline seminal examples of druggable

mutations and targeting modalities and address the clinical and research challenges that must be overcome to maximize therapeutic benefit.

CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES

NSCLC - SURGERY

[Outcome of thoracoscopic anatomical sublobar resection under 3-dimensional computed tomography simulation](#)

Surg Endosc. 2022 Apr;36(4):2312-2320. doi: 10.1007/s00464-021-08506-x. Epub 2021 Apr 21. Akira Hamada 1 , Hiroyuki Oizumi 2 , Hirohisa Kato 2 , Jun Suzuki 2 , Kenta Nakahashi 2 , Satoshi Takamori 2 , Ri Sho 3 , Mitsuaki Sadahiro 2

BACKGROUND: Previous studies have reported the feasibility and efficacy of thoracoscopic anatomical sublobar resection under three-dimensional computed tomography (3DCT) simulation; however, its long-term outcomes have not been clearly established in primary lung cancer. This study aimed to evaluate the long-term outcomes of this technique. **METHODS:** We retrospectively reviewed data from 112 consecutive patients with selected clinical stage IA non-small cell lung cancer (NSCLC) who underwent thoracoscopic anatomical sublobar resection from 2004 to 2014. This procedure was planned using preoperative 3DCT simulation to ensure sufficient surgical margins and enabled tailor-made surgery for each patient. Patients who had predominantly ground glass opacity lung cancers underwent anatomical sublobar resection as a curative-intent resection. Other patients who were high-risk candidates for lobectomy underwent anatomical sublobar resection as a compromised limited resection. **RESULTS:** Of the 112 cases, 82 had a curative-intent resection, while 30 had a compromised limited resection. Recurrence occurred in only 2 cases (1.8%), both of which were in the compromised limited group. A second primary lung cancer was observed in 5 cases (4.5%). Of the 5 patients, 4 underwent surgery for a second cancer and had no recurrence. The 5-year overall survival, lung cancer-specific overall survival, and recurrence-free survival rates were 92.5%, 100%, and 98.2%, respectively, for all cases; 97.6%, 100%, and 100%, respectively, in the curative-intent group; and 75.8%, 100% and 92.6%, respectively, in the compromised limited group. **CONCLUSIONS:** Thoracoscopic anatomical sublobar resection under 3DCT simulation may be an acceptable alternative treatment in selected patients with NSCLC.

[Application of Vagus Nerve Branch Preservation in Thoracoscopic Surgery for Early-Stage Lung Cancer](#)

Biomed Res Int. 2022 Apr 11;2022:5143383. doi: 10.1155/2022/5143383. eCollection 2022. Xiangzheng Liu 1 , Zhimao Chen 1 , Shijie Zhang 1

BACKGROUND: In this study, we introduced a novel surgical strategy to protect vagal nerve branches during radical thoracoscopic surgery in right lung cancer and explored the effects of vagal nerve branch preservation. **METHODS:** We retrospectively studied 53 patients with right-sided lung cancer with clinically staged T1N0M0 between 2019 and 2020. All 53 patients were treated with total thoracoscopic lobectomy and mediastinal lymph node dissection in the same number of lymph node stations. Of these, 22 patients adopted a vagus nerve branch protection strategy during lymph node dissection. Another 31 patients were treated with traditional lymph node dissection as the control group. **RESULTS:** The characteristics of the patients were similar between the two groups. The operation time and intraoperative bleeding in the protection group were longer than those in the control group. However, the protection group had a lower average postoperative pain score and average postoperative hospital stay. The above difference was not statistically significant. Three cases of arrhythmia occurred in the protection group, including 1 case of tachycardia and 2 cases of atrial fibrillation. In the control group, 13 cases of arrhythmia occurred after the operation, including 8 cases of tachycardia and 5 cases of atrial fibrillation. We also tracked changes in the patients' heart rates throughout the treatment process (excluding patients with arrhythmias). An increased heart rate was observed postoperatively in both groups, but the increase

of heart rate of the protection group was smaller than that of the control group; however, the difference was not statistically significant. **CONCLUSIONS:** A vagus nerve branch preservation-based approach to radical surgery is a safe and feasible strategy for right lung cancer treatment, which could significantly reduce the risk of postoperative arrhythmia in patients and may also have a potential role in reducing the length of hospital stay and maintaining heart rate stability in the postoperative period.

[Comparison of postoperative cough-related quality of life and recovery between sublobectomy and lobectomy for early-stage non-small cell lung cancer patients: a longitudinal study](#) BMC Pulm Med. 2022 Apr 23;22(1):154. doi: 10.1186/s12890-022-01954-8. Rongjia Lin # 1 , Wen Chen # 2 , Leilei Zhu 3 , Xiaojie Pan 4

BACKGROUND: Cough is a common complication after pulmonary surgery. Previous studies lacked a standard measure to assess postoperative cough-related quality of life and recovery. The purpose of this study is to compare postoperative cough regarding changes in health-related quality of life (HRQOL) and recovery trajectory between video-assisted thoracic surgery (VATS) lobectomy and sublobectomy (segmentectomy or wedge resection) for early-stage non-small cell lung cancer (NSCLC) patients via the Leicester Cough Questionnaire in Mandarin Chinese (LCQ-MC). **METHODS:** Overall, 156 patients with NSCLC underwent either VATS lobectomy or VATS sublobectomy; LCQ-MC was used to report the impact of postoperative cough on HRQOL for 6 months after surgery. The total scores of LCQ-MC range from 3 to 21, with a higher score indicating better health. Recovery from postoperative cough was defined as LCQ-MC scores returning to preoperative levels. The sensitivity of LCQ-MC to changes in postoperative cough recovery over time was evaluated via its ability to distinguish between surgery types. **RESULTS:** The VATS sublobectomy group reported significantly higher mean LCQ-MC scores at 1 month after surgery, but no significant difference postoperatively at 3 and 6 months after surgery, and returned to preoperative physical (69 vs. 99 days), psychological (67 vs. 99 days), social (50 vs. 98 days) and total (69 vs. 99 days) scores faster than the VATS lobectomy group (all $p < 0.05$). **CONCLUSION:** VATS sublobectomy had generally better HRQOL and faster recovery of postoperative cough than VATS lobectomy. In addition, the LCQ-MC performed satisfactorily in describing the longitudinal changes in postoperative cough.

[Propensity-matched Analysis Demonstrates Long-term Risk of Respiratory and Cardiac Mortality After Pneumonectomy Compared With Lobectomy for Lung Cancer](#) Ann Surg. 2022 Apr 1;275(4):793-799. doi: 10.1097/SLA.0000000000004065. Gregory D Jones 1 , Raul Caso 1 , Kay See Tan 2 3 , et al.

OBJECTIVE: We sought to quantify and characterize long-term consequences of pneumonectomy, with particular attention to nononcologic mortality. Summary of background data: Pneumonectomy is associated with profound changes in cardiopulmonary physiology. Studies of long-term outcomes after pneumonectomy typically report generalized measures, such as disease-free and overall survival. **METHODS:** Patients undergoing lobectomy or pneumonectomy for lung cancer at our institution from 2000 to 2018 were reviewed. Propensity-score matching was performed for 12 clinicopathologic factors. Ninety-day complications and deaths were compared. Five-year cumulative incidence of oncologic and nononcologic mortality were compared using competing risks approaches. **RESULTS:** From 3339 lobectomy and 355 pneumonectomy patients identified, we derived 318 matched pairs. At 90 days, rates of overall complications were similar (46% for pneumonectomy vs 43% for lobectomy; $P = 0.40$), but rates of major complications (21% vs 13%; $P = 0.005$) and deaths (6.9% vs 1.9%; $P = 0.002$) were higher the pneumonectomy cohort. The cumulative incidence of oncologic mortality was not significantly different between cohorts ($P = 0.9584$). However, the cumulative incidence of nononcologic mortality was substantially higher in the pneumonectomy cohort for both date of surgery and 1-year landmark analyses ($P < 0.0001$ and $P = 0.0002$, respectively). Forty-five pneumonectomy patients (18%) died of

nononcologic causes 1-5 years after surgery; pneumonia (n = 21) and myocardial infarction (n = 10) were the most common causes. In pneumonectomy patients, preexisting cardiac comorbidity and low diffusion capacity of the lungs for carbon monoxide were predictive of nononcologic mortality. **CONCLUSIONS:** Compared to lobectomy, excess mortality after pneumonectomy extends beyond 1 year and is driven primarily by nononcologic causes. Pneumonectomy patients require lifelong monitoring and may benefit from expeditious assessment and intervention at the initial signs of illness.

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

[Real-world usage of bevacizumab-bvzr biosimilar in US oncology practice](#) Am J Manag Care. 2022 Apr;28(4):160-166. doi: 10.37765/ajmc.2022.88831. Jingyan Yang ¹, John Mark Kelton, Jeffrey Thompson, Jose Maria Jimenez Alvir, Martine C Maculaitis, Ahmed Shelbaya

OBJECTIVES: Bevacizumab is commonly used to treat solid tumors. However, little is known about the manner and the extent to which bevacizumab biosimilars are utilized in real-world oncology practice in the United States. The objective of this study was to describe patient and provider characteristics and treatment patterns associated with the recently introduced bevacizumab-bvzr biosimilar. **STUDY DESIGN:** Retrospective cohort study. **METHODS:** A retrospective analysis of medical and pharmacy claims between January 24, 2019, and July 31, 2020, was performed. Adult patients with at least 1 claim indicating usage of bevacizumab-bvzr were included. Patients who could not be assigned to an applicable diagnosis group were excluded. Index treatment date was defined as the date of the first claim for bevacizumab-bvzr. Descriptive analysis was conducted for all study variables. **RESULTS:** A total of 206 patients were included; patients most often were 65 years or older (49.5%), were female (62.6%), and resided in the West (45.1%). The most common indications observed for bevacizumab-bvzr were metastatic colorectal cancer (mCRC; 51.0%), cancer of the female genital organs (CFG0; 27.2%), glioblastoma (11.2%), and non-small cell lung cancer (8.7%). Overall, 72.4% and 48.2% of patients with mCRC and CFG0, respectively, had switched to bevacizumab-bvzr from the reference drug or another bevacizumab biosimilar. Bevacizumab-bvzr was used in chemotherapy combination regimens for patients with mCRC and CFG0. **CONCLUSIONS:** Utilization was observed in extrapolated indications. Findings suggest that both switching between reference product and bevacizumab biosimilars and using bevacizumab-bvzr as part of chemotherapy combination regimens have been adopted in US oncology practice.

[Can Previous Chemotherapy Affect the Outcome of Nivolumab Treatment in Non-small Cell Lung Cancer?](#) Anticancer Res. 2022 Apr;42(4):1987-1995. doi: 10.21873/anticancer.15677. Martin Svaton ¹, Monika Bratova ², Leona Koubkova ³, Ondrej Fischer ⁴, et al.

AIM: This study compared the results of nivolumab treatment in patients with pulmonary adenocarcinomas based upon previous chemotherapeutic regimens. **PATIENTS AND METHODS:** The data source for this retrospective study was the Czech VILP registry of patients with nivolumab-treated adenocarcinomas in second and higher lines of treatment. In relation to objective response rate, progression-free interval, and overall survival, three comparisons of patient were made: A: Those treated in first line with cisplatin and pemetrexed versus carboplatin with paclitaxel or vinorelbine; B: treatment with cisplatin and pemetrexed versus carboplatin with paclitaxel/vinorelbine and bevacizumab; and C: treatment in previous lines with pemetrexed (first-line cisplatin and pemetrexed plus those treated in second line with pemetrexed) versus treatment with taxane (first-line carboplatin and paclitaxel only plus those treated with second-line docetaxel). **RESULTS:** We observed no differences in objective response rate or progression-free survival between patients treated with the stated chemotherapeutic regimens. We observed a trend towards better overall survival for patients treated with carboplatin plus taxanes or vinorelbine with/without bevacizumab. **CONCLUSION:** From our overall survival data, a

chemotherapeutic regimen of carboplatin plus taxanes or vinorelbine with/without bevacizumab might be a better partner for immunotherapy than a cisplatin and pemetrexed-based one.

[Assessment of hyperprogression versus the natural course of disease development with nivolumab with or without ipilimumab versus placebo in phase III, randomized, controlled trials](#) J Immunother Cancer. 2022 Apr;10(4):e004273. doi: 10.1136/jitc-2021-004273. Yoon-Koo Kang ¹, Martin Reck ², Paul Nghiem ³, et al.

BACKGROUND: Retrospective studies have suggested a potential risk of hyperprogressive disease (HPD) in patients receiving immune checkpoint inhibitors (ICIs). We compared the incidence of HPD during treatment with nivolumab±ipilimumab versus natural tumor progression with placebo in post hoc analyses of two randomized, double-blind clinical trials. **METHODS:** ATTRACTION-2 randomized patients with advanced gastric or gastroesophageal junction cancer (GC/GEJC) and progression on ≥2 prior regimens to nivolumab 3 mg/kg Q2W or placebo. CheckMate 451 randomized patients with extensive-disease small cell lung cancer (ED SCLC) and ongoing complete/partial response or stable disease after first-line chemotherapy to nivolumab 240 mg Q2W, nivolumab 1 mg/kg+ipilimumab 3 mg/kg Q3W for four doses then nivolumab 240 mg Q2W, or placebo. Patients receiving ≥1 dose of study drug and with tumor scans at baseline and the first on-treatment evaluation were included in the HPD analyses. HPD definitions were ≥20%, ≥50%, and ≥100% increase in target lesion sum of the longest diameters (SLD) at the first on-treatment assessment. **RESULTS:** In the ATTRACTION-2 HPD-evaluable population, 243 patients received nivolumab and 115 placebo. Fewer patients receiving nivolumab versus placebo had increases in SLD ≥20% (33.7% vs 46.1%) and ≥50% (6.2% vs 11.3%); similar proportions had increases in SLD ≥100% (1.6% vs 1.7%). In the CheckMate 451 HPD-evaluable population, 177 patients received nivolumab, 179 nivolumab+ipilimumab, and 175 placebo. Fewer patients receiving nivolumab or nivolumab+ipilimumab versus placebo had increases in SLD ≥20% (27.1%, 27.4% vs 45.7%), ≥50% (10.2%, 11.2% vs 22.3%), and ≥100% (2.8%, 2.8% vs 6.3%). **CONCLUSIONS:** Nivolumab±ipilimumab was not associated with an increased rate of progression versus placebo in patients with GC, GEJC, or ED SCLC, suggesting that previous reports of HPD may reflect the natural disease course in some patients rather than ICI-mediated progression.

[Real-world Afatinib Outcomes in Advanced Non-small Cell Lung Cancer Harboring EGFR Mutations](#) Anticancer Res. 2022 Apr;42(4):2145-2157. doi: 10.21873/anticancer.15697.

Chi-Han Chen ^{1 2}, John Wen-Cheng Chang ^{2 3}, et al.

BACKGROUND/AIM: Afatinib is a standard treatment for patients with advanced non-small cell lung cancer (NSCLC) harboring epidermal growth factor receptor (EGFR) mutations. Osimertinib can overcome the treatment resistance-associated EGFR T790M mutation, and the sequence of afatinib followed by osimertinib is an effective therapeutic strategy for NSCLC patients. This study comprehensively evaluated the outcomes of sequential therapy following frontline afatinib and identified predictive factors for T790M mutation acquisition. **PATIENTS AND METHODS:** Data from patients with advanced NSCLC treated with frontline afatinib at a Taiwanese hospital group from June 2014 to March 2018 were retrospectively reviewed. The EGFR T790M mutation was detected by tissue sequencing or liquid biopsy. The patients' clinicopathological features were collected, and univariate and multivariate analyses were performed to identify potential predictive and prognostic factors. **RESULTS:** A total of 635 patients treated with afatinib were enrolled in this study. Until August 2021, 553 patients experienced progression, and 225 patients underwent T790M mutation testing. The T790M positive rate was 54.2%. Both exon 19 deletion and progression-free survival were associated with T790M positivity. Osimertinib was found to be effective in T790M-positive but not T790M-negative NSCLC. The median overall survival (OS) was 61.8 months for patients with T790M mutation undergoing later-line osimertinib compared with 30.1 months for patients without T790M mutation undergoing chemotherapy

only. Osimertinib independently prolonged OS after afatinib progression. **CONCLUSION:** This study confirmed the efficacy of sequential afatinib and osimertinib treatment. T790M mutation detection and osimertinib availability are important for prolonging survival in patients with NSCLC harboring EGFR mutations.

Sotorasib: a treatment for non-small cell lung cancer with the KRAS G12C mutation Drugs Today (Barc). 2022 Apr;58(4):175-185. doi: 10.1358/dot.2022.58.4.3400573. Xinting Zheng # 1 , Jiamin Luo # 2 , Wei Liu 1 , Charles R Ashby Jr 3 , Zhe-Sheng Chen 4 5 , Lizhu Lin 6
Sotorasib, a direct inhibitor of the enzyme Kirsten rat sarcoma viral oncogene (KRAS) with the G12C mutation, was approved by the U.S. Food and Drug Administration (FDA), as a second-line treatment for locally advanced or metastatic non-small cell lung cancer (NSCLC) containing the KRAS G12C mutation, on the basis of results of a phase II clinical trial (Code- BreK100). In this article, we review the mechanism of action of KRAS G12C inhibitors and the latest clinical trials with sotorasib to provide a comprehensive understanding of its efficacy and toxicity. We also review the mechanisms that produce resistance to the KRAS G12C inhibitors and the preclinical research related to combination treatments for KRAS G12C-mutated tumors. Currently, clinical data suggests that sotorasib monotherapy has significant efficacy in NSCLC patients with the KRAS G12C mutation and tolerable toxicity, and it could represent a novel targeted therapy. Additional research will be required to delineate the mechanisms of resistance to sotorasib and determine the efficacy and safety of combination therapy for the treatment of NSCLC containing the KRAS G12C mutation.

Durvalumab after chemoradiotherapy for locally advanced non-small cell lung cancer prolonged distant metastasis-free survival, progression-free survival and overall survival in clinical practice BMC Cancer. 2022 Apr 4;22(1):364. doi: 10.1186/s12885-022-09354-1. Takaya Yamamoto 1 , Yoko Tsukita 2 , Yu Katagiri 3 , et al.

BACKGROUND: In clinical practice, the effect of durvalumab and radiation pneumonitis (RP) on survival after intensity-modulated radiotherapy (IMRT) is not fully understood. The purpose of this retrospective study was to investigate factors related to distant metastasis-free survival (DMFS), progression-free survival (PFS) and overall survival (OS) after IMRT for locally advanced non-small cell lung cancer (LA-NSCLC). **METHODS:** All patients who were treated with conventional fractionated IMRT for LA-NSCLC between April 2016 and March 2021 were eligible. Time-to-event data were assessed by using the Kaplan-Meier estimator, and the Cox proportional hazards model was used for prognostic factor analyses. Factors that emerged after the start of IMRT, such as durvalumab administration or the development of RP, were analysed as time-dependent covariates. **RESULTS:** A total of 68 consecutive patients treated with conventional fractionated IMRT for LA-NSCLC were analysed. Sixty-six patients completed radiotherapy, 50 patients received concurrent chemotherapy, and 36 patients received adjuvant durvalumab. During the median follow-up period of 14.3 months, 23 patients died, and tumour progression occurred in 37 patients, including 28 patients with distant metastases. The 1-year DMFS rate, PFS rate and OS rate were 59.9%, 48.7% and 84.2%, respectively. Grade 2 RP occurred in 16 patients, grade 3 in 6 patients and grade 5 in 1 patient. The 1-year cumulative incidences of grade 2 or higher RP and grade 3 or higher RP were 33.8% and 10.3%, respectively. The results of multivariate analyses showed that durvalumab had a significantly lower hazard ratio (HR) for DMFS, PFS and OS (HR 0.31, $p < 0.01$; HR 0.33, $p < 0.01$ and HR 0.32, $p = 0.02$), respectively. Grade 2 or higher RP showed significance for DMFS and a nonsignificant trend for OS (HR 2.28, $p = 0.04$ and HR 2.12, $p = 0.13$), respectively, whereas a higher percentage of lung volume receiving 20 Gy or higher was significant for PFS (HR 2.25, $p = 0.01$). **CONCLUSIONS:** In clinical practice, durvalumab administration following IMRT with concomitant chemotherapy showed a significant survival benefit. Reducing the risk of grade 2 or higher RP would also be beneficial.

[Updated Integrated Analysis of the Efficacy and Safety of Entrectinib in Patients With NTRK Fusion-Positive Solid Tumors](#) Clin Cancer Res. 2022 Apr 1;28(7):1302-1312. doi: 10.1158/1078-

0432.CCR-21-3597. George D Demetri¹, Filippo De Braud^{2,3}, Alexander Drilon⁴, et al.

PURPOSE: Entrectinib potently inhibits tropomyosin receptor kinases (TRKAs)/B/C and ROS1, and previously induced deep [objective response rate (ORR) 57.4%] and durable [median duration of response (DoR) 10.4 months] responses in adults with NTRK fusion-positive solid tumors from three phase I/II trials. This article expands prior reports with additional patients and longer follow-up.

Patients and METHODS: Patients with locally advanced/metastatic NTRK fusion-positive solid tumors and ≥ 12 months' follow-up were included. Primary endpoints were ORR and DoR by blinded independent central review (BICR); secondary endpoints included progression-free survival (PFS), intracranial efficacy, and safety. The safety-evaluable populations included all patients who had received ≥ 1 entrectinib dose. **RESULTS:** At clinical cut-off (August 31, 2020), the efficacy-evaluable population comprised 121 adults with 14 tumor types and ≥ 30 histologies. Median follow-up was 25.8 months; 61.2% of patients had a complete (n = 19) or partial response (n = 55). Median DoR was 20.0 months [95% confidence interval (CI), 13.0-38.2]; median PFS was 13.8 months (95% CI, 10.1-19.9). In 11 patients with BICR-assessed measurable central nervous system (CNS) disease, intracranial ORR was 63.6% (95% CI, 30.8-89.1) and median intracranial DoR was 22.1 (95% CI, 7.4-not estimable) months. The safety profile of entrectinib in adults and pediatric patients was aligned with previous reports. Most treatment-related adverse events (TRAEs) were grade 1/2 and manageable/reversible with dose modifications. TRAE-related discontinuations occurred in 8.3% of patients. **CONCLUSIONS:** With additional clinical experience, entrectinib continues to demonstrate durable systemic and intracranial responses and can address the unmet need of a CNS-active treatment in patients with NTRK fusion-positive solid tumors.

[Association of a novel 27-gene immuno-oncology assay with efficacy of immune checkpoint inhibitors in advanced non-small cell lung cancer](#) BMC Cancer. 2022 Apr 14;22(1):407. doi:

10.1186/s12885-022-09470-y. Harsha Ranganath¹, Amit L Jain¹, Justin R Smith¹, et al.

BACKGROUND: Immune checkpoint inhibitor (ICI) therapies represent a major advance in treating a variety of advanced-stage malignancies. Nevertheless, only a subset of patients benefit, even when selected based on approved biomarkers such as PD-L1 and tumor mutational burden. New biomarkers are needed to maximize the therapeutic ratio of these therapies. **METHODS:** In this retrospective cohort, we assessed a 27-gene RT-qPCR immuno-oncology (IO) gene expression assay of the tumor immune microenvironment and determined its association with the efficacy of ICI therapy in 67 advanced-stage NSCLC patients. The 27-gene IO test score (IO score), programmed cell death ligand 1 immunohistochemistry tumor proportion score (PD-L1 TPS), and tumor mutational burden (TMB) were analyzed as continuous variables for response and as binary variables for one-year progression free survival. The threshold for the IO score was prospectively set based upon a previously described training cohort. Prognostic implications of the IO score were evaluated in a separate cohort of 104 advanced-stage NSCLC patients from The Cancer Genome Atlas (TCGA) who received non-ICI therapy. **RESULTS:** The IO score was significantly different between responders or non-responders (p = 0.007) and associated with progression-free survival (p = 0.001). Bivariate analysis established that the IO score was independent of PD-L1 TPS and TMB in identifying patients benefiting from ICI therapy. In a separate cohort of late-stage NSCLC patients from TCGA, the IO score was not prognostic of outcome from non-ICI-treated patients. **CONCLUSIONS:** This study is the first application of this 27-gene IO RT-qPCR assay in a clinical cohort with outcome data. IO scores were significantly associated with response to ICI therapy and prolonged progression-free survival. Together, these data suggest the IO score should be further studied to define its role in informing clinical decision-making for ICI treatment in NSCLC.

[Dual checkpoint targeting of B7-H3 and PD-1 with enoblituzumab and pembrolizumab in advanced solid tumors: interim results from a multicenter phase I/II trial](#) J Immunother Cancer. 2022

Apr;10(4):e004424. doi: 10.1136/jitc-2021-004424. Charu Aggarwal¹, Amy Prawira², Scott Antonia³, et al.

BACKGROUND: Availability of checkpoint inhibitors has created a paradigm shift in the management of patients with solid tumors. Despite this, most patients do not respond to immunotherapy, and there is considerable interest in developing combination therapies to improve response rates and outcomes. B7-H3 (CD276) is a member of the B7 family of cell surface molecules and provides an alternative immune checkpoint molecule to therapeutically target alone or in combination with programmed cell death-1 (PD-1)-targeted therapies. Enoblituzumab, an investigational anti-B7-H3 humanized monoclonal antibody, incorporates an immunoglobulin G1 fragment crystallizable (Fc) domain that enhances Fc γ receptor-mediated antibody-dependent cellular cytotoxicity. Coordinated engagement of innate and adaptive immunity by targeting distinct members of the B7 family (B7-H3 and PD-1) is hypothesized to provide greater antitumor activity than either agent alone. **METHODS:** In this phase I/II study, patients received intravenous enoblituzumab (3-15 mg/kg) weekly plus intravenous pembrolizumab (2 mg/kg) every 3 weeks during dose-escalation and cohort expansion. Expansion cohorts included non-small cell lung cancer (NSCLC; checkpoint inhibitor [CPI]-naïve and post-CPI, programmed death-ligand 1 [PD-L1] <1%), head and neck squamous cell carcinoma (HNSCC; CPI-naïve), urothelial cancer (post-CPI), and melanoma (post-CPI). Disease was assessed using Response Evaluation Criteria in Solid Tumors version 1.1 after 6 weeks and every 9 weeks thereafter. Safety and pharmacokinetic data were provided for all enrolled patients; efficacy data focused on HNSCC and NSCLC cohorts. **RESULTS:** Overall, 133 patients were enrolled and received ≥ 1 dose of study treatment. The maximum tolerated dose of enoblituzumab with pembrolizumab at 2 mg/kg was not reached. Intravenous enoblituzumab (15 mg/kg) every 3 weeks plus pembrolizumab (2 mg/kg) every 3 weeks was recommended for phase II evaluation. Treatment-related adverse events occurred in 116 patients (87.2%) and were grade ≥ 3 in 28.6%. One treatment-related death occurred (pneumonitis). Objective responses occurred in 6 of 18 (33.3% [95% CI 13.3 to 59.0]) patients with CPI-naïve HNSCC and in 5 of 14 (35.7% [95% CI 12.8 to 64.9]) patients with CPI-naïve NSCLC. **CONCLUSIONS:** Checkpoint targeting with enoblituzumab and pembrolizumab demonstrated acceptable safety and antitumor activity in patients with CPI-naïve HNSCC and NSCLC.

NSCLC - RADIOTHERAPY

[Estimating the Probability of Not Completing the Intended Course of Thoracic Radiotherapy for Lung Cancer](#) Anticancer Res. 2022 Apr;42(4):1973-1977. doi: 10.21873/anticancer.15675. Dirk Rades¹

Esther Glatzel², Sabine Bohnet³, Steven E Schild⁴, Elisa M Werner²

BACKGROUND/AIM: In some patients with lung cancer scheduled for thoracic radiotherapy (RT), treatment is discontinued before reaching the planned dose. For optimal treatment personalization, a tool estimating whether a patient can complete radiotherapy would be helpful. **PATIENTS AND METHODS:** Eleven pre-RT characteristics were analyzed in 170 patients receiving local RT for lung cancer. Characteristics included age, sex, tumor site, histology, tumor and nodal stage, distant metastasis, surgery, systemic treatment, pulmonary function, and smoking history. **RESULTS:** Age >75 years (p=0.038), distant metastasis (p=0.009), and forced expiratory volume in 1 second <1.2 l (p=0.038) were significantly associated with discontinuation of RT. A prognostic instrument was developed in 126 patients with complete data regarding these characteristics. It included three groups (0, 1, and 2-3 points) with non-completion rates of 33.3%, 55.0% and 75.0% (p=0.004). **CONCLUSION:** This new instrument can help estimating the probability that lung cancer patients assigned to local RT cannot complete the planned course of RT.

From Postoperative to Preoperative: A Case Series of Hypofractionated and Single-Fraction Neoadjuvant Stereotactic Radiosurgery for Brain Metastases

Oper Neurosurg (Hagerstown). 2022 Apr 1;22(4):208-214. doi: 10.1227/ONS.000000000000101. Cristian Udovicich 1 2, Sweet Ping Ng 3, Damien Tange 4, Nola Bailey 5, Neda Haghighi 1 5

BACKGROUND: Postoperative stereotactic radiosurgery after resection of brain metastases is currently the standard of care. However, rates of leptomeningeal disease (LMD) after postoperative stereotactic radiosurgery have been reported to be >30%. Neoadjuvant stereotactic radiosurgery (NaSRS) has been proposed as an alternative treatment approach to decrease this risk. **OBJECTIVE:** To report the local control (LC) and LMD rates in patients undergoing NaSRS. **METHODS:** Our retrospective multicenter case series included consecutive patients planned for SRS followed by resection of intracranial lesions with a confirmed primary malignancy. Concurrent SRS alone to other intracranial lesions was permitted. Exclusion criteria included previous local treatment to that particular lesion and Eastern Cooperative Oncology Group performance status ≥ 3 . Outcomes reported included LC, distant intracranial control (DC), overall survival, LMD, and radionecrosis (RN) rates. **RESULTS:** Overall, 28 patients with 29 lesions were eligible for analysis. The median follow-up was 12.8 months. The mean age was 62.5 (range 43-80) years, and 55% were Eastern Cooperative Oncology Group performance status 0 to 1. The most common primary malignancies included non-small cell lung cancer (43%) and melanoma (32%). Hypofractionated SRS was used in 62.1%. The 12-month LC and LMD rates were 91.3% and 4.0%, respectively. The 12-month RN, DC, and overall survival rates were 5.0%, 51.5%, and 60.1%, respectively. **CONCLUSION:** Compared with postoperative SRS, our study suggests that NaSRS leads to comparable local control with a decreased risk of LMD and RN. This is the first NaSRS series with a majority of patients treated with fractionated SRS. NaSRS is a promising approach for appropriate patients where surgical resection is a component of local therapy.

Patterns of Use of Stereotactic Body Radiation Therapy Compared With Surgery for Definitive Treatment of Primary Early-stage Non-small Cell Lung Cancer

Am J Clin Oncol. 2022 Apr 1;45(4):146-154. doi: 10.1097/COC.0000000000000902. Julie K Jang 1, Scott M Atay 2, Li Ding 3, Elizabeth A David 2, Sean C Wightman 2, Anthony W Kim 2, Jason C Ye 1

OBJECTIVE: As stereotactic body radiation therapy (SBRT) becomes widely available for early-stage non-small cell lung cancer (NSCLC), there may be concerns in the surgical community that SBRT is being offered for patients with operable tumors, even though surgery is standard of care. We evaluated the trends in SBRT and surgery over time for patients with NSCLC. **METHODS:** The National Cancer Database was queried for patients with node-negative NSCLC ≤ 5 cm from 2004 to 2016. The relationships between definitive local treatment modalities and year were analyzed using a multinomial regression model while controlling for other covariates. **RESULTS:** Among the 202,367 patients who met the inclusion criteria, there was a steady decrease in mean tumor size in all treatment modalities, from 2.44 cm (SD=1.08) to 2.25 cm (SD=1.00) over the study period. In the multinomial model, the probability of receiving lobectomy demonstrated a slight decline from 58% (2004) to 53% (2016). The use of SBRT increased from 1% to 20%, while patients receiving no therapy declined from 27% to 16%. The likelihood of SBRT increased with year of diagnosis ($P < 0.0001$) and decreasing tumor size ($P < 0.0001$), compared with lobectomy. Age, race, income, facility, and Charlson-Deyo score were also associated with treatment modality. **CONCLUSIONS:** The mean tumor size of early-stage NSCLC decreased over the study period for all treatment modalities. SBRT use has increased, mostly among older patients with smaller tumors and Charlson-Deyo scores ≥ 3 . The increase in SBRT contributed to the significant decline in patients who had no therapy.

[Expression and Clinicopathological Significance of SOX11 in Small-Cell Lung Cancer](#) Biomed Res Int. 2022 Mar 30;2022:1707914. doi: 10.1155/2022/1707914. eCollection 2022. Wang Xinli 1 , Wang Lixiao 2 , Ding Baoqi 1 , Huang Hu 1 , Zhang Qiang 2

OBJECTIVE: This study aims to investigate the expression of neuronal transcription factor SOX11 in small-cell lung cancer (SCLC) and compare it with the expression of CD56 (nerve cell adhesion molecule), synaptophysin (Syn), chromogranin A (CgA), and thyroid transcription factor-1 (TTF-1) to explore the application value of SOX11 in the pathological diagnosis of SCLC. **METHODS:** Immunohistochemical methods were used to detect the expression of SOX11, TTF-1, CD56, Syn, and CgA in 120 lung tumor tissues, and experimental results were analyzed using SPSS23.0 statistical software. **RESULTS:** Immunohistochemical results showed that in the 120 lung tumor samples, SOX11 was highly expressed in SCLC and localized to the nucleus, with low or no expression in control carcinoid/lung neuroendocrine tumors, lung adenocarcinomas, and lung squamous cell carcinomas. Statistical analysis results revealed the following points. First, the expression of SOX11 was closely related to the tumor histological type. The expression of SOX11 in SCLC (positive rate of 63.33%) was significantly higher than that in carcinoid/neuroendocrine tumors (positive rate of 12.50%), lung adenocarcinoma (positive rate of 0%), and lung squamous cell carcinoma (positive rate of 0%). Second, immunohistochemical investigation of 60 SCLC cases revealed that the highest positive rates of CD56, TTF-1, and Syn, respectively, were 93.33 percent, 95 percent, and 86.67 percent. SOX11 also exhibited high sensitivity (0.633) and specificity (0.875) in SCLC. The positive rates of SOX11 and CgA were 63.33% and 50.00%, respectively. Statistical results revealed that the positive rate of CgA had no significant difference ($P > 0.05$). Lastly, the combined use of antibodies SOX11, CgA, CD56, Syn, and TTF-1 was more beneficial to improving the diagnosis rate of SCLC than the single use of one or two antibodies. **CONCLUSION:** The expression of SOX11 in different histological types of lung tumors differs considerably. SOX11 is highly expressed in SCLC. SOX11 can be used as a beneficial supplement to the combination of classical neuroendocrine markers and in combination with CgA, CD56, Syn, and TTF-1 to assist in the diagnosis of SCLC.

[Heterogeneity of neuroendocrine transcriptional states in metastatic small cell lung cancers and patient-derived models](#) Nat Commun. 2022 Apr 19;13(1):2023. doi: 10.1038/s41467-022-29517-9.

Delphine Lissa # 1 , Nobuyuki Takahashi # 2 3 , et al.

Molecular subtypes of small cell lung cancer (SCLC) defined by the expression of key transcription regulators have recently been proposed in cell lines and limited number of primary tumors. The clinical and biological implications of neuroendocrine (NE) subtypes in metastatic SCLC, and the extent to which they vary within and between patient tumors and in patient-derived models is not known. We integrate histology, transcriptome, exome, and treatment outcomes of SCLC from a range of metastatic sites, revealing complex intra- and intertumoral heterogeneity of NE differentiation. Transcriptomic analysis confirms previously described subtypes based on ASCL1, NEUROD1, POU2F3, YAP1, and ATOH1 expression, and reveal a clinical subtype with hybrid NE and non-NE phenotypes, marked by chemotherapy-resistance and exceedingly poor outcomes. NE tumors are more likely to have RB1, NOTCH, and chromatin modifier gene mutations, upregulation of DNA damage response genes, and are more likely to respond to replication stress targeted therapies. In contrast, patients preferentially benefited from immunotherapy if their tumors were non-NE. Transcriptional phenotypes strongly skew towards the NE state in patient-derived model systems, an observation that was confirmed in paired patient-matched tumors and xenografts. We provide a framework that unifies transcriptomic and genomic dimensions of metastatic SCLC. The marked differences in transcriptional diversity between patient tumors and model systems are likely to have implications in development of novel therapeutic agents.

[Genomic and transcriptomic analysis of a library of small cell lung cancer patient-derived xenografts](#)

Nat Commun. 2022 Apr 19;13(1):2144. doi: 10.1038/s41467-022-29794-4. Rebecca Caesar 1, Jacklynn V Egger 1, Shweta Chavan 1, et al.

Access to clinically relevant small cell lung cancer (SCLC) tissue is limited because surgical resection is rare in metastatic SCLC. Patient-derived xenografts (PDX) and circulating tumor cell-derived xenografts (CDX) have emerged as valuable tools to characterize SCLC. Here, we present a resource of 46 extensively annotated PDX/CDX models derived from 33 patients with SCLC. We perform multi-omic analyses, using targeted tumor next-generation sequencing, RNA-sequencing, and immunohistochemistry to deconvolute the mutational landscapes, global expression profiles, and molecular subtypes of these SCLC models. SCLC subtypes characterized by transcriptional regulators, ASCL1, NEUROD1 and POU2F3 are confirmed in this cohort. A subset of SCLC clinical specimens, including matched PDX/CDX and clinical specimen pairs, confirm that the primary features and genomic and proteomic landscapes of the tumors of origin are preserved in the derivative PDX models. This resource provides a powerful system to study SCLC biology.

PALLIATIVE AND SUPPORTIVE CARE

[Optimising Outcomes in Non Small Cell Lung Cancer: Targeting Cancer Cachexia](#)

Front Biosci (Landmark Ed). 2022 Apr 18;27(4):129. doi: 10.31083/j.fbl2704129. Iain Phillips 1 2, Mark Stares 1 2, Lindsay Allan 3, Judith Sayers 4, Richard Skipworth 5, Barry Laird 1 4

Lung cancer is the commonest malignancy worldwide and the leading cause of cancer death. Half of patients with lung cancer present with advanced disease. The number of systemic therapies including immunotherapy and targeted treatment are rapidly increasing. Despite this, the outcomes for many patients with locally advanced and advanced lung cancer are poor, as many patients are too unwell for treatment. One of the reasons patients with Non-Small Cell Lung Cancer are not fit for treatment is cancer cachexia, which is common (upto 75% of patients) in this group. This metabolic syndrome presents clinically as weight loss (muscle +/- fat), decreased physical function (patients less active) and anorexia on a background of systemic inflammation. Currently there is not an optimal management pathway for these patients, however, there is emerging data that multi-modal intervention including nutritional support, physical training and pharmacological therapy may have a role in treating cachexia. This review discusses assessment and intervention in cancer cachexia.

[Effect of a Symptom Monitoring Intervention for Patients Hospitalized With Advanced Cancer: A Randomized Clinical Trial](#)

JAMA Oncol. 2022 Apr 1;8(4):571-578. doi: 10.1001/jamaoncol.2021.7643. Ryan D Nipp 1, Nora K Horick 2, Carolyn L Qian 1, et al.

IMPORTANCE: Symptom monitoring interventions are increasingly becoming the standard of care in oncology, but studies assessing these interventions in the hospital setting are lacking. **OBJECTIVE:** To evaluate the effect of a symptom monitoring intervention on symptom burden and health care use among hospitalized patients with advanced cancer. **DESIGN, SETTING, AND PARTICIPANTS:** This nonblinded randomized clinical trial conducted from February 12, 2018, to October 30, 2019, assessed 321 hospitalized adult patients with advanced cancer and admitted to the inpatient oncology services of an academic hospital. Data obtained through November 13, 2020, were included in analyses, and all analyses assessed the intent-to-treat population. **INTERVENTIONS:** Patients in both the intervention and usual care groups reported their symptoms using the Edmonton Symptom Assessment System (ESAS) and the 4-item Patient Health Questionnaire-4 (PHQ-4) daily via tablet computers. Patients assigned to the intervention had their symptom reports displayed during daily oncology rounds, with alerts for moderate,

severe, or worsening symptoms. Patients assigned to usual care did not have their symptom reports displayed to their clinical teams. **MAIN OUTCOMES AND MEASURES:** The primary outcome was the proportion of days with improved symptoms, and the secondary outcomes were hospital length of stay and readmission rates. Linear regression was used to evaluate differences in hospital length of stay. Competing-risk regression (with death treated as a competing event) was used to compare differences in time to first unplanned readmission within 30 days. **RESULTS:** From February 12, 2018, to October 30, 2019, 390 patients (76.2% enrollment rate) were randomized. Study analyses to assess change in symptom burden included 321 of 390 patients (82.3%) who had 2 or more days of symptom reports completed (usual care, 161 of 193; intervention, 160 of 197). Participants had a mean (SD) age of 63.6 (12.8) years and were mostly male (180; 56.1%), self-reported as White (291; 90.7%), and married (230; 71.7%). The most common cancer type was gastrointestinal (118 patients; 36.8%), followed by lung (60 patients; 18.7%), genitourinary (39 patients; 12.1%), and breast (29 patients; 9.0%). No significant differences were detected between the intervention and usual care for the proportion of days with improved ESAS-physical (unstandardized coefficient [B] = -0.02; 95% CI, -0.10 to 0.05; P = .56), ESAS-total (B = -0.05; 95% CI, -0.12 to 0.02; P = .17), PHQ-4-depression (B = -0.02; 95% CI, -0.08 to 0.04; P = .55), and PHQ-4-anxiety (B = -0.04; 95% CI, -0.10 to 0.03; P = .29) symptoms. Intervention patients also did not differ significantly from patients receiving usual care for the secondary end points of hospital length of stay (7.59 vs 7.47 days; B = 0.13; 95% CI, -1.04 to 1.29; P = .83) and 30-day readmission rates (26.5% vs 33.8%; hazard ratio, 0.73; 95% CI, 0.48-1.09; P = .12). **CONCLUSIONS AND RELEVANCE:** This randomized clinical trial found that for hospitalized patients with advanced cancer, the assessed symptom monitoring intervention did not have a significant effect on patients' symptom burden or health care use. These findings do not support the routine integration of this type of symptom monitoring intervention for hospitalized patients with advanced cancer.

[Early specialized palliative care for patients with metastatic lung cancer receiving chemotherapy: a feasibility study of a nurse-led screening-triggered programme](#) Jpn J Clin Oncol. 2022 Apr 6;52(4):375-382. doi: 10.1093/jjco/hyab204. Yoshihisa Matsumoto¹, Shigeki Umemura², Ayumi Okizaki^{3,4}, et al.

BACKGROUND: Strategies to implement early specialized palliative care have not yet been established. The present study investigated the feasibility of a nurse-led, screening-triggered early specialized palliative care intervention programme and obtained data to design a randomized controlled trial. **METHODS:** Patients with metastatic lung cancer undergoing first-line platinum-based chemotherapy were eligible. The intervention consisted of (1) a questionnaire-based screening programme and (2) advanced-level nurse counselling and care coordination with interdisciplinary team approach. The primary endpoint was the completion rate of the assessment questionnaire after the second course of first-line chemotherapy (T2). Secondary endpoints included changes in Functional Assessment of Cancer Therapy-Lung scores, depression and anxiety rates based on the Patient Health Questionnaire 9 and the Hospital Anxiety and Depression Scale, and the contents of specialized palliative care. **RESULTS:** A total of 50 patients were enrolled between August 2012 and March 2014. Median age was 66 years (range, 40-78 year) and 84% were male. A total of 38 patients had stage IV non-small cell lung carcinoma and 12 had extensive disease small-cell lung carcinoma. The completion rate was 70% (95% confidence interval 56.0-81.0). The median duration between baseline and T2 was 53 days. Improvement from baseline were observed at T2 in Functional Assessment of Cancer Therapy-Lung scores (86.0 ± 18.1 vs 94.9 ± 18.2 , P = 0.057), depression (16.0 vs 5.7%; P = 0.26) and anxiety (32.0 vs 22.9%; P = 0.65); however, these results were not statistically significant. **CONCLUSIONS:** This early specialized palliative care intervention is feasible and could be useful in improving patients' quality of life. The present results justify the initiation of a randomized control trial.

[Checkpoint Inhibitor Pneumonitis Induced by Anti-PD-1/PD-L1 Therapy in Non-Small-Cell Lung Cancer: Occurrence and Mechanism](#) Front Immunol. 2022 Apr 7;13:830631. doi:

10.3389/fimmu.2022.830631. eCollection 2022. Jianqiong Yin 1, Yuanjun Wu 1, Xue Yang 1, Lu Gan 2, Jianxin Xue 1 3 4

Immune checkpoint inhibitors (ICIs), particularly those targeting programmed death 1 (PD-1) and anti-programmed death ligand 1 (PD-L1), enhance the antitumor effect by restoring the function of the inhibited effector T cells and produce durable responses in a large variety of metastatic and late patients with non-small-cell lung cancer. Although often well tolerated, the activation of the immune system results in side effects known as immune-related adverse events (irAEs), which can affect multiple organ systems, including the lungs. The occurrence of severe pulmonary irAEs, especially checkpoint inhibitor pneumonitis (CIP), is rare but has extremely high mortality and often overlaps with the respiratory symptoms and imaging of primary tumors. The development of CIP may be accompanied by radiation pneumonia and infectious pneumonia, leading to the simultaneous occurrence of a mixture of several types of inflammation in the lungs. However, there is a lack of authoritative diagnosis, grading criteria and clarified mechanisms of CIP. In this article, we review the incidence and median time to onset of CIP in patients with non-small-cell lung cancer treated with PD-1/PD-L1 blockade in clinical studies. We also summarize the clinical features, potential mechanisms, management and predictive biomarkers of CIP caused by PD-1/PD-L1 blockade in non-small-cell lung cancer treatment.

[A Prognostic Tool to Estimate the Risk of Pneumonitis in Patients Irradiated for Lung Cancer](#)

Anticancer Res. 2022 Apr;42(4):2029-2032. doi: 10.21873/anticancerres.15683. Esther Glatzel 1, Elisa M Werner 1, Sabine Bohnet 2, Dirk Rades 3

BACKGROUND/AIM: Radiotherapy of lung cancer can lead to pneumonitis. This study aimed to identify risk factors and create a prognostic tool. **PATIENTS AND METHODS:** Sixteen factors were evaluated in 169 patients irradiated for lung cancer including age, sex, lung function, primary tumor/nodal stage, histology, tumor location, surgery, systemic treatment, radiation volume, total dose, mean dose to ipsilateral lung, history of another malignancy, pack years, chronic inflammatory disease, and cardiovascular disease. **RESULTS:** Forty-one patients experienced pneumonitis. Significant associations were found for total doses >56 Gy (p=0.023), mean lung doses >20 Gy (p=0.002) or >13 Gy (p<0.001), and chronic inflammatory disease (p=0.034). Considering mean lung dose and chronic inflammatory disease, scores were 2, 3, 4, or 5 points. Pneumonitis rates were 0% (0/35), 24% (14/58), 32% (21/66), and 60% (6/10) (p=0.001), respectively. **CONCLUSION:** Based on significant risk factors, a prognostic tool was developed that can help estimate the risk of pneumonitis and contribute to personalized follow up of patients.

[Patterns of Use of Stereotactic Body Radiation Therapy Compared With Surgery for Definitive Treatment of Primary Early-stage Non-small Cell Lung Cancer](#) Am J Clin Oncol. 2022 Apr

1;45(4):146-154. doi: 10.1097/COC.0000000000000902. Julie K Jang 1, Scott M Atay 2, Li Ding 3, Elizabeth A David 2, Sean C Wightman 2, Anthony W Kim 2, Jason C Ye 1

OBJECTIVE: As stereotactic body radiation therapy (SBRT) becomes widely available for early-stage non-small cell lung cancer (NSCLC), there may be concerns in the surgical community that SBRT is being offered for patients with operable tumors, even though surgery is standard of care. We evaluated the trends in SBRT and surgery over time for patients with NSCLC. **MATERIALS AND METHODS:** The National Cancer Database was queried for patients with node-negative NSCLC ≤5 cm from 2004 to 2016. The relationships between definitive local treatment modalities and year were analyzed using a multinomial regression model while controlling for other covariates. **RESULTS:** Among the 202,367 patients who met the inclusion criteria, there was a steady decrease in mean tumor size in all treatment modalities, from 2.44 cm (SD=1.08) to 2.25 cm (SD=1.00) over the study period. In the multinomial

model, the probability of receiving lobectomy demonstrated a slight decline from 58% (2004) to 53% (2016). The use of SBRT increased from 1% to 20%, while patients receiving no therapy declined from 27% to 16%. The likelihood of SBRT increased with year of diagnosis ($P<0.0001$) and decreasing tumor size ($P<0.0001$), compared with lobectomy. Age, race, income, facility, and Charlson-Deyo score were also associated with treatment modality. **CONCLUSIONS:** The mean tumor size of early-stage NSCLC decreased over the study period for all treatment modalities. SBRT use has increased, mostly among older patients with smaller tumors and Charlson-Deyo scores ≥ 3 . The increase in SBRT contributed to the significant decline in patients who had no therapy.

[From Postoperative to Preoperative: A Case Series of Hypofractionated and Single-Fraction Neoadjuvant Stereotactic Radiosurgery for Brain Metastases](#)

Oper Neurosurg (Hagerstown). 2022 Apr 1;22(4):208-214. doi: 10.1227/ONS.000000000000101. Cristian Udovicich 1 2 , Sweet Ping Ng 3 , Damien Tange 4 , Nola Bailey 5 , Neda Haghighi 1 5

BACKGROUND: Postoperative stereotactic radiosurgery after resection of brain metastases is currently the standard of care. However, rates of leptomeningeal disease (LMD) after postoperative stereotactic radiosurgery have been reported to be $>30\%$. Neoadjuvant stereotactic radiosurgery (NaSRS) has been proposed as an alternative treatment approach to decrease this risk. **OBJECTIVE:** To report the local control (LC) and LMD rates in patients undergoing NaSRS. **METHODS:** Our retrospective multicenter case series included consecutive patients planned for SRS followed by resection of intracranial lesions with a confirmed primary malignancy. Concurrent SRS alone to other intracranial lesions was permitted. Exclusion criteria included previous local treatment to that particular lesion and Eastern Cooperative Oncology Group performance status ≥ 3 . Outcomes reported included LC, distant intracranial control (DC), overall survival, LMD, and radionecrosis (RN) rates. **RESULTS:** Overall, 28 patients with 29 lesions were eligible for analysis. The median follow-up was 12.8 months. The mean age was 62.5 (range 43-80) years, and 55% were Eastern Cooperative Oncology Group performance status 0 to 1. The most common primary malignancies included non-small cell lung cancer (43%) and melanoma (32%). Hypofractionated SRS was used in 62.1%. The 12-month LC and LMD rates were 91.3% and 4.0%, respectively. The 12-month RN, DC, and overall survival rates were 5.0%, 51.5%, and 60.1%, respectively. **CONCLUSION:** Compared with postoperative SRS, our study suggests that NaSRS leads to comparable local control with a decreased risk of LMD and RN. This is the first NaSRS series with a majority of patients treated with fractionated SRS. NaSRS is a promising approach for appropriate patients where surgical resection is a component of local therapy.

[Comparison of postoperative cough-related quality of life and recovery between sublobectomy and lobectomy for early-stage non-small cell lung cancer patients: a longitudinal study](#)

BMC Pulm Med. 2022 Apr 23;22(1):154. doi: 10.1186/s12890-022-01954-8. Rongjia Lin # 1 , Wen Chen # 2 , Leilei Zhu 3 , Xiaojie Pan 4

BACKGROUND: Cough is a common complication after pulmonary surgery. Previous studies lacked a standard measure to assess postoperative cough-related quality of life and recovery. The purpose of this study is to compare postoperative cough regarding changes in health-related quality of life (HRQOL) and recovery trajectory between video-assisted thoracic surgery (VATS) lobectomy and sublobectomy (segmentectomy or wedge resection) for early-stage non-small cell lung cancer (NSCLC) patients via the Leicester Cough Questionnaire in Mandarin Chinese (LCQ-MC). **METHODS:** Overall, 156 patients with NSCLC underwent either VATS lobectomy or VATS sublobectomy; LCQ-MC was used to report the impact of postoperative cough on HRQOL for 6 months after surgery. The total scores of LCQ-MC range from 3 to 21, with a higher score indicating better health. Recovery from postoperative cough was defined as LCQ-MC scores returning to preoperative levels. The sensitivity of LCQ-MC to changes in postoperative cough recovery over time was evaluated via its ability to distinguish between surgery types.

RESULTS: The VATS sublobectomy group reported significantly higher mean LCQ-MC scores at 1 month after surgery, but no significant difference postoperatively at 3 and 6 months after surgery, and returned to preoperative physical (69 vs. 99 days), psychological (67 vs. 99 days), social (50 vs. 98 days) and total (69 vs. 99 days) scores faster than the VATS lobectomy group (all $p < 0.05$). **CONCLUSION:** VATS sublobectomy had generally better HRQOL and faster recovery of postoperative cough than VATS lobectomy. In addition, the LCQ-MC performed satisfactorily in describing the longitudinal changes in postoperative cough.

[Palliative Radiation for Advanced Central Lung Tumors With Intentional Avoidance of the Esophagus \(PROACTIVE\): A Phase 3 Randomized Clinical Trial](#) JAMA Oncol. 2022 Apr 1;8(4):1-7. doi: 10.1001/jamaoncol.2021.7664. Alexander V Louie 1 2 , Patrick V Granton 3 , Alysa Fairchild 4 , et al.

IMPORTANCE: Palliative thoracic radiotherapy (RT) can alleviate local symptoms associated with advanced non-small cell lung cancer (NSCLC), but esophagitis is a common treatment-related adverse event. Whether esophageal-sparing intensity-modulated RT (ES-IMRT) achieves a clinically relevant reduction in esophageal symptoms remains unclear. **OBJECTIVE:** To examine whether ES-IMRT achieves a clinically relevant reduction in esophageal symptoms compared with standard RT. Design, setting, and participants: Palliative Radiation for Advanced Central Lung Tumors With Intentional Avoidance of the Esophagus (PROACTIVE) is a multicenter phase 3 randomized clinical trial that enrolled patients between June 24, 2016, and March 6, 2019. Data analysis was conducted from January 23, 2020, to October 22, 2021. Patients had up to 1 year of follow-up. Ninety patients at 6 tertiary academic cancer centers who had stage III/IV NSCLC and were eligible for palliative thoracic RT (20 Gy in 5 fractions or 30 Gy in 10 fractions) were included. **INTERVENTIONS:** Patients were randomized (1:1) to standard RT (control arm) or ES-IMRT. Target coverage was compromised to ensure the maximum esophagus dose was no more than 80% of the RT prescription dose. **MAIN OUTCOMES AND MEASURES:** The primary outcome was esophageal quality of life (QOL) 2 weeks post-RT, measured by the esophageal cancer subscale (ECS) of the Functional Assessment of Cancer Therapy: Esophagus questionnaire. Higher esophageal cancer subscale scores correspond with improved QOL, with a 2- to 3-point change considered clinically meaningful. Secondary outcomes included overall survival, toxic events, and other QOL metrics. Intention-to-treat analysis was used. **RESULTS:** Between June 24, 2016, and March 6, 2019, 90 patients were randomized to standard RT or ES-IMRT (median age at randomization, 72.0 years [IQR, 65.6-80.3]; 50 [56%] were female). Thirty-six patients (40%) received 20 Gy and 54 (60%) received 30 Gy. For the primary end point, the mean (SD) 2-week ECS score was 50.5 (10.2) in the control arm (95% CI, 47.2-53.8) and 54.3 (7.6) in the ES-IMRT arm (95% CI, 51.9-56.7) ($P = .06$). Symptomatic RT-associated esophagitis occurred in 24% ($n = 11$) of patients in the control arm vs 2% ($n = 1$) in the ES-IMRT arm ($P = .002$). In a post hoc subgroup analysis based on the stratification factor, reduction in esophagitis was most evident in patients receiving 30 Gy (30% [$n = 8$] vs 0%; $P = .004$). Overall survival was similar with standard RT (median, 8.6; 95% CI, 5.7-15.6 months) and ES-IMRT (median, 8.7; 95% CI, 5.1-10.2 months) ($P = .62$). **CONCLUSIONS AND RELEVANCE:** In this phase 3 randomized clinical trial, ES-IMRT did not significantly improve esophageal QOL but significantly reduced the incidence of symptomatic esophagitis. Because post hoc analysis found that reduced esophagitis was most evident in patients receiving 30 Gy of RT, these findings suggest that ES-IMRT may be most beneficial when the prescription dose is higher (30 Gy).

COMPLEMENTARY & ALTERNATIVE THERAPY

[The Root Extract of Peucedanum praeruptorum Dunn Exerts Anticancer Effects in Human Non-Small-Cell Lung Cancer Cells with Different EGFR Mutation Statuses by Suppressing MET](#)

[Activity](#) *Molecules*. 2022 Apr 6;27(7):2360. doi: 10.3390/molecules27072360. Hyun-Ji Park 1 , Jae-Hoon Jeong 1 , Shin-Hyung Park 1

The aim of this study was to investigate the anticancer effects of the root extract of *Peucedanum praeruptorum* Dunn (EPP) in human non-small-cell lung cancer (NSCLC) cells and explore the mechanisms of action. We used four types of human lung cancer cell lines, including H1299 (epidermal growth factor receptor (EGFR) wild-type), PC9 (EGFR Glu746-Ala750 deletion mutation in exon 19; EGFR tyrosine kinase inhibitor (TKI)-sensitive), H1975 (EGFR L858R/T790M double-mutant; EGFR TKI-resistant), and PC9/ER (erlotinib-resistant) cells. EPP suppressed cell growth and the colony formation of NSCLC cells in a concentration-dependent manner. EPP stimulated chromatin condensation, increased the percentage of sub-G1 phase cells, and enhanced the proportion of annexin V-positive cells, demonstrating that EPP triggered apoptosis in NSCLC cells regardless of the EGFR mutation and EGFR TKI resistance status. The phosphorylation level of the signal transducer and activator of transcription 3 (STAT3) and AKT was decreased by EPP. The expression of STAT3 target genes was also downregulated by EPP. EPP reversed hepatocyte growth factor (HGF)-induced MET phosphorylation and gefitinib resistance. Taken together, our results demonstrate that EPP exerted anticancer effects not only in EGFR TKI-sensitive NSCLC cells, but also in EGFR TKI-resistant NSCLC cells, by suppressing MET activity.

[Osmundacetone modulates mitochondrial metabolism in non-small cell lung cancer cells by hijacking the glutamine/glutamate/ \$\alpha\$ -KG metabolic axis](#) *Phytomedicine*. 2022 Jun;100:154075. doi: 10.1016/j.phymed.2022.154075. Epub 2022 Apr 4. Yue Yang 1 , Pingya He 1 , Yuhao Hou 1 , Zhicheng Liu 1 , Xiaoping Zhang 1 , Ning Li 2

BACKGROUND: Osmundacetone (OSC) is a bioactive phenolic compound isolated from *Phellinus igniarius* and that was shown to exert cytotoxic effects on cancer cells in our previous work. The antiproliferative impact of OSC on non-small cell lung cancer (NSCLC) and the underlying mechanisms, however, have not been studied. **PURPOSE:** This study aimed to explore the antiproliferative effect of OSC on NSCLC cells and the mechanisms involved. **METHODS:** Cell viability, colony formation and cell cycle distribution were measured following exposure to OSC in vitro. The anticancer activity of OSC was also examined using a xenograft growth assay in vivo. Furthermore, serum metabolomics analysis by GC-MS was done to detect alterations in the metabolic profile. Next, expression of GLS1 and GLUD1, the key enzymes in glutamine metabolism, was evaluated using RT-PCR and western blot. α -KG and NADH metabolites were assessed by ELISA. Mitochondrial functions and morphology were evaluated using the JC-1 probe and transmission electron microscopy, respectively. The ATP production rate in mitochondria of cells with OSC treatment was determined using a Seahorse XFe24 Analyzer. **RESULTS:** OSC selectively reduced the proliferation of A549 and H460 cells. OSC triggered G2/M cell cycle arrest and decreased the cell clone formation. A mouse xenograft model revealed that OSC inhibited tumor growth in vivo. Findings of serum metabolomics analyses indicated that the anticancer function of OSC was related to disorders of glutamine metabolism. Such a speculation was further verified by the expression level of GLUD1, which was downregulated by OSC treatment. Concentrations of the related metabolites α -KG and NADH were reduced in response to OSC treatment. Moreover, OSC led to disorganization of the mitochondrial ultrastructure and a decrease in mitochondrial membrane potential. OSC also decreased ATP production via oxidative phosphorylation (OXPHOS) but did not affect glycolysis in NSCLC cells. **CONCLUSION:** The key role of OSC in mitochondrial energy metabolism in NSCLC cells is to suppress tumor development and cell proliferation downregulating GLUD1 to inhibit the glutamine/glutamate/ α -KG metabolic axis and OXPHOS. It indicates that OSC might be a potential natural agent for personalized medicine and an anticancer metabolic modulator in NSCLC chemotherapy.

[Pulmonary Tuberculosis and the Incidence of Lung Cancer among Patients with Chronic Obstructive Pulmonary Disease](#) Ann Am Thorac Soc. 2022 Apr;19(4):640-648. doi:

10.1513/AnnalsATS.202010-1240OC. Hye Yun Park 1, Danbee Kang 2 3, Sun Hye Shin 1, Hayoung Choi 4, Seung Hun Jang 5, Chang-Hoon Lee 6, Hojoong Kim 1, O Jung Kwon 1, Chin Kook Rhee 7, Juhee Cho 2 3 8

RATIONALE: Although a history of pulmonary tuberculosis (PTB) is a risk factor for developing both chronic obstructive pulmonary disease (COPD) and lung cancer, it remains unclear whether a history of PTB affects lung cancer development in patients with COPD. **OBJECTIVES:** To investigate whether a history of PTB is associated with an increased risk of lung cancer development in a population with COPD. **METHODS:** This cohort study included a nationwide representative sample of 13,165 Korean men and women with COPD, aged between 50 and 84 years. In addition, to assess whether the relationship between PTB and lung cancer risk differs between participants with and without COPD, a matched cohort without COPD was included. Participants were matched 1:3 for age, sex, smoking history, and PTB status based on the index health screening examination of corresponding participants with COPD. The two cohorts were followed up for 13 years (January 1, 2003, to December 31, 2015). PTB was diagnosed on the basis of the results of chest radiography, and incident lung cancer was identified from hospitalization and outpatient visit claims (International Classification of Diseases, Tenth Revision diagnosis code C33 or C34). **RESULTS:** During 370,617 person-years (PY) of follow-up (median follow-up, 7.7 yr) in the COPD group, we observed 430 incident cases of lung cancer in participants without a history of PTB (incidence rate, 524 per 100,000 PY) and 148 cases in those with a history of PTB (incidence rate, 931 per 100,000 PY). Compared with participants without a PTB history, the fully adjusted subdistribution hazard ratio (95% confidence interval [CI]) for lung cancer in those with a history of PTB was 1.24 (1.03-1.50). The association of PTB history and lung cancer development was more evident in never-smokers with COPD. In contrast, among participants without COPD, the corresponding hazard ratio (95% CI) was 0.98 (0.78-1.22). There was no interaction among PTB, smoking status, and COPD. **CONCLUSIONS:** A history of PTB was associated with an increased risk of developing lung cancer among patients with COPD in our country with an intermediate tuberculosis burden. Patients with COPD with a history of PTB, particularly never-smokers, might benefit from periodic screening or assessment for lung cancer development.

[The Survival Impact of Second Primary Lung Cancer in Patients With Lung Cancer](#) J Natl Cancer Inst. 2022 Apr 11;114(4):618-625. doi: 10.1093/jnci/djab224. Eunji Choi 1, Sophia J Luo 1, Jacqueline V Aredo 2, et al.

BACKGROUND: Lung cancer survivors have a high risk of developing second primary lung cancer (SPLC), but little is known about the survival impact of SPLC diagnosis. **METHODS:** We analyzed data from 138 969 patients in the Surveillance, Epidemiology, and End Results (SEER), who were surgically treated for initial primary lung cancer (IPLC) in 1988-2013. Each patient was followed from the date of IPLC diagnosis to SPLC diagnosis (for those with SPLC) and last vital status through 2016. We performed multivariable Cox regression to evaluate the association between overall survival and SPLC diagnosis as a time-varying predictor. To investigate potential effect modification, we tested interaction between SPLC and IPLC stage. Using data from the Multiethnic Cohort Study (MEC) (n = 1540 IPLC patients with surgery), we evaluated the survival impact of SPLC by smoking status. All statistical tests were 2-sided. **RESULTS:** A total of 12 115 (8.7%) patients developed SPLC in SEER over 700 421 person-years of follow-up. Compared with patients with single primary lung cancer, those with SPLC had statistically significantly reduced overall survival (hazard ratio [HR] = 2.12, 95% confidence interval [CI] = 2.06 to 2.17; P < .001). The effect of SPLC on reduced survival was more pronounced among patients

with early stage IPLC vs advanced-stage IPLC (HR = 2.14, 95% CI = 2.08 to 2.20, vs HR = 1.43, 95% CI = 1.21 to 1.70, respectively; Pinteraction < .001). Analysis using MEC data showed that the effect of SPLC on reduced survival was statistically significantly larger among persons who actively smoked at initial diagnosis vs those who formerly or never smoked (HR = 2.31, 95% CI = 1.48 to 3.61, vs HR = 1.41, 95% CI = 0.98 to 2.03, respectively; Pinteraction = .04). **CONCLUSIONS:** SPLC diagnosis is statistically significantly associated with decreased survival in SEER and MEC. Intensive surveillance targeting patients with early stage IPLC and active smoking at IPLC diagnosis may lead to a larger survival benefit.

Utilization and costs of epidermal growth factor receptor mutation testing and targeted therapy in Medicare patients with metastatic lung adenocarcinoma BMC Health Serv Res. 2022 Apr

9;22(1):470. doi: 10.1186/s12913-022-07857-y. Chan Shen 1 2 3 , Rolfy A Perez Holguin 4 , Eric Schaefer 5 , Shouhao Zhou 5 6 , Chandra P Belani 6 7 , Patrick C Ma 6 7 , Michael F Reed 4 6

BACKGROUND: Guidelines in 2013 and 2014 recommended Epidermal Growth Factor Receptor (EGFR) testing for metastatic lung adenocarcinoma patients as the efficacy of targeted therapies depends on the mutations. However, adherence to these guidelines and the corresponding costs have not been well-studied. **METHODS:** We identified 2362 patients at least 65 years old newly diagnosed with metastatic lung adenocarcinoma from January 2013 to December 2015 using the SEER-Medicare database. We examined the utilization patterns of EGFR testing and targeted therapies including erlotinib and afatinib. We further examined the costs of both EGFR testing and targeted therapy in terms of Medicare costs and patient out-of-pocket (OOP) costs. **RESULTS:** The EGFR testing rate increased from 38% in 2013 to 51% and 49% in 2014 and 2015 respectively. The testing rate was 54% among the 394 patients who received erlotinib, and 52% among the 42 patients who received afatinib. The median Medicare and OOP costs for testing were \$1483 and \$293. In contrast, the costs for targeted therapy were substantially higher with median 30-day costs at \$6114 and \$240 for erlotinib and \$6239 and \$471 for afatinib. **CONCLUSION:** This population-based study suggests that testing guidelines improved the use of EGFR testing, although there was still a large proportion of patients receiving targeted therapy without testing. The costs of targeted therapy were substantially higher than the testing costs, highlighting the need to improve adherence to testing guidelines in order to improve clinical outcomes while reducing the economic burden for both Medicare and patients.

Novel Program Offering Remote, Asynchronous Subspecialist Input in Thoracic Oncology: Early Experience and Insights Gained During the COVID-19 Pandemic JCO Oncol Pract. 2022

Apr;18(4):e537-e550. doi: 10.1200/OP.21.00339. Epub 2021 Dec 3. Howard Jack West 1 2 , Yuan Angela Tan 2 , Afsaneh Barzi 1 2 , Debra Wong 1 2 , Robert Parsley 2 , Todd Sachs 2

PURPOSE: AccessHope is a program developed initially by City of Hope to provide remote subspecialist input on cancer care for patients as a supplemental benefit for specific payers or employers. The leading platform for this work has been an asynchronous model of review of medical records followed by a detailed assessment of past and current management along with discussion of potential future options in a report sent to the local oncologist. This summary describes an early period of development and growth of this service, focusing on cases of lung cancer, particularly during the COVID-19 pandemic. **METHODS:** Cases were primarily identified by a trigger list of cancer diagnoses that included non-small-cell lung cancer and small-cell lung cancer. After medical records were obtained, a summary narrative was provided to a thoracic oncology specialist who wrote a case review sent to the local physician, followed by a direct discussion with the recipient. We focused on feasibility as measured by case volumes, the rates of concordance between the subspecialist reviewer with the local team, and cost savings from recommended changes, using descriptive statistics. **RESULTS:** From April 2019 to November 2020, 110 cases were reviewed: 55% male, median age 62.5 years (range, 33-92 years); 82%

non-small-cell lung cancer (12% stage I or II, 16% stage III, and 57% stage IV), and 17% small-cell lung cancer (4% limited and 14% extensive). Median turnaround time for report send-out was 5.0 days. The review agreed with local management in 79 (72%) cases and disagreed in 31 (28%) cases; notably, specific additional recommendations were associated with evidence-based anticipated improvements in efficacy in 76 cases (69%) and improvement in potential for cure in 14 cases (13%). Recommendations leading to cost savings were identified in 14 cases (13%), translating to a projected cost savings of \$19,062 (USD) per patient for the entire cohort of patient cases reviewed. **CONCLUSION:** We demonstrate the feasibility of completing a rapid turnaround of cases of lung cancer either patient-initiated for review or prospectively triggered by diagnosis and stage. This program of asynchronous second opinions identified evidence-based management changes affecting current treatment in 28% and potential improvements to improve care in 92% of patients, along with cost savings realized by eliminating low-value interventions.

[Demographic Differences Among US Department of Veterans Affairs Patients Referred for Genetic Consultation to a Centralized VA Telehealth Program, VA Medical Centers, or the Community](#)

JAMA Netw Open. 2022 Apr 1;5(4):e226687. doi: 10.1001/jamanetworkopen.2022.6687.

Maren T Scheuner^{1, 2}, Alexis K Huynh³, Catherine Chanfreau-Coffinier⁴, et al.

IMPORTANCE: Telehealth enables access to genetics clinicians, but impact on care coordination is unknown. **OBJECTIVE:** To assess care coordination and equity of genetic care delivered by centralized telehealth and traditional genetic care models. **DESIGN, SETTING, AND PARTICIPANTS:** This cross-sectional study included patients referred for genetic consultation from 2010 to 2017 with 2 years of follow-up in the US Department of Veterans Affairs (VA) health care system. Patients were excluded if they were referred for research, cytogenetic, or infectious disease testing, or if their care model could not be determined. **EXPOSURES:** Genetic care models, which included VA-telehealth (ie, a centralized team of genetic counselors serving VA facilities nationwide), VA-traditional (ie, a regional service by clinical geneticists and genetic counselors), and non-VA care (ie, community care purchased by the VA). **MAIN OUTCOMES AND MEASURES:** Multivariate regression models were used to assess associations between patient and consultation characteristics and the type of genetic care model referral; consultation completion; and having 0, 1, or 2 or more cancer surveillance (eg, colonoscopy) and risk-reducing procedures (eg, bilateral mastectomy) within 2 years following referral. **RESULTS:** In this study, 24 778 patients with genetics referrals were identified, including 12 671 women (51.1%), 13 193 patients aged 50 years or older (53.2%), 15 639 White patients (63.1%), and 15 438 patients with cancer-related referrals (62.3%). The VA-telehealth model received 14 580 of the 24 778 consultations (58.8%). Asian patients, American Indian or Alaskan Native patients, and Hawaiian or Pacific Islander patients were less likely to be referred to VA-telehealth than White patients (OR, 0.54; 95% CI, 0.35-0.84) compared with the VA-traditional model. Completing consultations was less likely with non-VA care than the VA-traditional model (OR, 0.45; 95% CI, 0.35-0.57); there were no differences in completing consultations between the VA models. Black patients were less likely to complete consultations than White patients (OR, 0.84; 95% CI, 0.76-0.93), but only if referred to the VA-telehealth model. Patients were more likely to have multiple cancer preventive procedures if they completed their consultations (OR, 1.55; 95% CI, 1.40-1.72) but only if their consultations were completed with the VA-traditional model. **CONCLUSIONS AND RELEVANCE:** In this cross-sectional study, the VA-telehealth model was associated with improved access to genetics clinicians but also with exacerbated health care disparities and hindered care coordination. Addressing structural barriers and the needs and preferences of vulnerable subpopulations may complement the centralized telehealth approach, improve care coordination, and help mitigate health care disparities.

Risk of SARS-CoV2-Related Mortality in Non-Small Cell Lung Cancer Patients Treated with First-Line Immunotherapy Alone or in Combination with Chemotherapy Cancer Invest. 2022

May;40(5):406-412. doi: 10.1080/07357907.2021.1970761. Epub 2022 Apr 6. Giuseppe Luigi Banna 1 , Ornella Cantale 2 , Alex Friedlaender 3 , Harliana Yusof 1 , Shyamika Acharige 1 , Alfredo Addeo 3
BACKGROUND: The impact of systemic anticancer treatments on SARS-CoV-2-related mortality is still debatable. **METHODS:** By a retrospective analysis of patients with non-small-cell lung cancer (NSCLC) treated with first-line Pembrolizumab or in combination with chemotherapy (ChT) during the first surge of the pandemic. **RESULTS:** The adjusted risk of death was higher in patients treated with ChT + Pembrolizumab (HR 4.6, 1.2-17.4, p = 0.02). The SARS-CoV-2-related mortality rate was higher in patients treated with ChT + Pembrolizumab (p = 0.03), ≥70 years (p = 0.03) and current smokers (p = 0.17). **CONCLUSIONS:** The addition of ChT to immunotherapy could be associated with increased risk of mortality and higher SARS-CoV-2-related mortality rate.

Variation in targetable genomic alterations in non-small cell lung cancer by genetic ancestry, sex, smoking history, and histology Genome Med. 2022 Apr 15;14(1):39. doi: 10.1186/s13073-022-01041-x.

Elio Adib # 1 2 , Amin H Nassar # 1 2 , Sarah Abou Alaiwi 1 2 , et al.

BACKGROUND: Genomic alterations in 8 genes are now the targets of FDA-approved therapeutics in non-small cell lung cancer (NSCLC), but their distribution according to genetic ancestry, sex, histology, and smoking is not well established. **METHODS:** Using multi-institutional genetic testing data from GENIE, we characterize the distribution of targetable genomic alterations in 8 genes among 8675 patients with NSCLC (discovery cohort: DFCI, N = 3115; validation cohort: Duke, Memorial Sloan Kettering Cancer Center, Vanderbilt, N = 5560). For the discovery cohort, we impute genetic ancestry from tumor-only sequencing and identify differences in the frequency of targetable alterations across ancestral groups, smoking pack-years, and histologic subtypes. **RESULTS:** We identified variation in the prevalence of KRASG12C, sensitizing EGFR mutations, MET alterations, ALK, and ROS1 fusions according to the number of smoking pack-years. A novel method for computing continental (African, Asian, European) and Ashkenazi Jewish ancestries from panel sequencing enables quantitative analysis of the correlation between ancestry and mutation rates. This analysis identifies a correlation between Asian ancestry and EGFR mutations and an anti-correlation between Asian ancestry and KRASG12C mutation. It uncovers 2.7-fold enrichment for MET exon 14 skipping mutations and amplifications in patients of Ashkenazi Jewish ancestry. Among never/light smokers, targetable alterations in LUAD are significantly enriched in those with Asian (80%) versus African (49%) and European (55%) ancestry. Finally, we show that 5% of patients with squamous cell carcinoma (LUSC) and 17% of patients with large cell carcinoma (LCLC) harbor targetable alterations. **CONCLUSIONS:** Among patients with NSCLC, there was significant variability in the prevalence of targetable genomic alterations according to genetic ancestry, histology, and smoking. Patients with LUSC and LCLC have 5% rates of targetable alterations supporting consideration for sequencing in those subtypes.